EVALUATION OF THE CRITICAL PARAMETERS AND POLYMERIC COAT PERFORMACE IN COMPRESSED MULTIPARTICULATE SYSTEMS

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Abstract

Compression of coated pellets is a practical alternative to capsule filling. The current practice is to add cushioning agents to minimize the stress on the coated pellets. Cushioning agents however add bulkiness and reduce the overall drug loading capacity. In this study, we investigated the performance of compressed coated pellets with no cushioning agent to evaluate the feasibility of predicting the coat behaviour using thermo-mechanical and rheological analysis techniques. Different coating formulations were made of ethyl cellulose (EC) as a coating polymer and two different kinds of additives were incorporated into the polymeric coating solution. Triethyl Citrate (TEC) and Polyethylene glycol 400(PEG400) were used as plasticizers at different levels to the coating formulations (10%, 20%, 30%). Thermal, mechanical and rheological measurements of the coating film formulations were achieved to investigate the effect of plasticizers. Thermal gravimetric analysis results (TGA) showed higher residual moisture content in films plasticised with PEG 400 compared to their TEC counterparts. Differential Scanning Calorimetry (DSC), Dynamic Mechanical Analysis (DMA) and Parallel Plate Shear Rheometer (PPSR) were used to study the influence of the level and type of plasticisers incorporated in coating film formulation on the performance of the coating film. In this study, both DSC and DMA were

used to investigate the Tg for each film coating formulation in order to evaluate the effect of the additives. In general DMA results for the Tg value of the films were always higher by 10-20% than those measured by the DSC. Furthermore, clamp size and the frequency of the oscillation have an influence on the evaluation of Tg. Complex viscosity for different coating film formulations revealed that the shear hinning gradient changes with temperature and plasticiser type and concentration. The value of complex viscosity from DMA and PPSR exhibits power law behaviour. The rheological moduli were indirectly affected by the level of plasticiser. There was a discrepancy between the complex viscosity results obtained from both DMA and PPSR at similar temperature but they follow the same trend. The non plasticized polymer showed a 10 time higher complex viscosity values when measured by DMA over that measured by PPSR. The difference was smaller in plasticized films but it was not consistent. Therefore a consistent coefficient to correlate the DMA and PPSR couldn't be accurately determined Coated pellets were compressed and key process parameters were evaluated. The obtained results revealed that the coating thickness has a significant effect on the release profile of the final products. It was found that by increasing the coating film thickness, the percentage released decreased. Also the compression force has lower influence on the drug release profile, while the dwell time has very low effect on the percentage release from the final products. Optimum release profile was obtained at a coating level of 5.5% w/w and a compression force of 4700N

In conclusion, the elasticity of the plasticised EC films in this study meant that the internal stress is not dissipated during compression and the dwell

time range that was used in this experiment. Increasing the thickness therefore was necessary to enhance the strength of the film and avoid cracking. The mechanical and rheological profiling was helpful therefore to understand the behaviour of the coated pellets and predict the film properties at various steps of the process of coating and compression (i.e., various shear rate regimes). Experimental design approach to studying the key process and formulation parameters helped identify the optimum values for the process.

PUBLICATIONS, COMMUNICATIONS and CONFERENCES

- Abrahem M. Abrahem, I. Grimsey, M. De-Matas, **Characterization of mechanical and thermal properties of ethyl cellulose as a film coating polymer for compressed pellets**, poster presentation, European Science Conference on Process Analytical Technology (EuPAT4) in Kuopio, Finland (May 2010)
- Poster presentation, PharmaSci conference in Nottingham, UK (Sept 2010)
- Abrahem M. Abrahem, I. Grimsey, M. De-Matas, **Study of the thermal and mechanical properties of a film coating polymer for use in tabletted pelletized systems**, poster presentation at the AAPS Conference, New Orleans, U.S.A. (Nov 2010)
- Attended UV Imaging Annual Symposium Bradford, UK (May 2011)
- Attended, PharmaSci conference in Nottingham, UK (Sept 2011)
- Abrahem M. Abrahem[1], I. Grimsey[1], T. Gough[2], M. Isreb[1], M. De Matas[3] **Comparative study to evaluate the performance of DMA vs. DSC and the Rheometer to study the thermal-mechanical and rheological properties of polymer coating film** Oral presentation, EuPAT5, Ghent, Belgium (May 2012)
- Abrahem M. Abrahem1, I. Grimsey1, T. Gough2, M. Isreb1, M. De Matas3, **Study of the Mechanical, Thermal and Rheological Properties of Ethyl Cellulose as a Film Coating Polymer** Poster presentation, Controlled Release Society (CRS), Quebec, Canada (July 2012)

- Abrahem M. Abrahem1, I. Grimsey1, T. Gough2, M. Isreb1, M. De Matas3, **A study of the mechanical and rheological properties of ethyl cellulose films using DMA, DSC and Rheometry** Poster Presentation, the AAPS 2012, Chicago, IL (Oct 2012)
- Member at American Association of Pharmaceutical Scientists (AAPS) for 2010, 2011, 2012, and 2013
- Member at the Controlled Release Society (CRS) 2012
- Abrahem M. Abrahem, I. Grimsey, T. Gough, **Study of the effect of manufacturing variables on the drug release and correlations to the mechanical properties of a coating film**. A poster presentation that has been accepted at AAPS 2013, San Antonio, Texas (Nov 2013).

List of Abbreviations

TEC	Trithyl citrate
EC	Ethylcellulose
PEG400	Polyethylene Glycol 400
TGA	Thermal gravimetric analysis
DSC	Differential scanning calorimetry
DMA	Dynamic mechanical analysis
PPSR	Parallel plate shear rheometer
Tg	Glass transition temperature
API	Active pharmaceutical ingredient
MUPS	Multiparticulate system
HPMC	Hydroxypropyl methylcellulose
MCC	Microcrystalline cellulose
G’	Storage modulus
G”	Loss modulus
G	Complex viscosity
SEM	Scanning electron microscopic

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I take great pride in this accomplishment and in being surrounded by such competent and dedicated people.

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Chapter 1: Introduction

1. Chapter: Introduction

This chapter provides an insight into the Multiple Units Pellets systems, their advantages and the challenges in the production process. It will delve into further details about the manufacturing steps and processes as well as the characteristics of the polymeric materials used to coat these MUPs. The chapter will end with a quick review of the rheological and mechanical properties of the polymers, the current gap in the literature, the rationale for the current study and finally the aims and objectives.

1.1 Oral controlled release dosage forms

The term controlled release has been used to describe a variety of dosage forms designed to slow or modify the release of drug and to distinguish the preparation from those that releases the drug immediately or offload it within a short time period (less that 15 min). There are various reasons for requiring the modification of the onset and the rate of drug release including reduction of the number of doses, decrease of the frequency of administration, reduced side effects and improved patient compliance (Torrado and Augsburger, 2008). Oral controlled release systems are designed in single (e.g. tablets) or multiple units (e.g. pellets) surrounded by a semipermeable matrix or membrane (coat). The latter is considered a safer and a more reproducible option (Alderborn, 2013).

1.2 Pellets: A general overview

The multiple unit approach to controlling drug release can be designed using various dosage form units including aggregated particles, microspheres, microcapsules, millispheres, beads and pellets. Pellets can be defined pharmaceutically as spherical particles produced by multiple compaction processes of wet granulation and extrusion of drug(s), binders and fillers then shaped into sphere by the process of spheronization. The spheres are usually produced in a size range from 0.5 to 1.5 mm. The excipients play important role to help the wet mass to plastically deform into the final pellets. In another word, these additives transform the mechanical compression energy of the granulation and extrusion steps into heat energy during the rearrangement of the polymer chains of these excipients (Kranz et al, 2009) (Abdul et al, 2010)

1.3 Multiple Unit pellet system(s)

After the pellets are produced through the extrusion and spheronization process, they are typically film coated if they are designed to deliver a controlled release of the drug. The pellets are then usually packaged in multiple Unit pellet system(s) (MUPs) which are easier to dispense and be handled by the patient. Pellets are typically either pressed into tablets or filled in capsules.

MUPs offer several advantages compared to single unit tablets. Firstly the spherical shape and the higher density of the pellets translate into better flowability than powders or even granules. This allows for a superior

uniformity of content in the final dosage form. Moreover the small size of the pellets provides a more uniform distribution into the gastrointestinal tract and that leads to improve the bioavailability of the drug. The release of the drug from multiple units also lead to minimizing the side effects of some drugs such as ulceration of the gastrointestinal tract. Moreover, because each pellet contains a fraction of the overall dose of the drug, the failure of some pellets does not mean the failure of the whole system. This reduces the risk of dose dumping. (Abdul et al, 2010) (Muley et al, 2016) (Kuang et al, 2017)

While direct compression into tablets offers a simpler and cost effective approach, the film could be deformed or ruptured and this could eventually affect the release profile of the medication. Therefore, in order to avoid compromising the performance of the dosage form, efforts are directed to alleviate this problem either by developing the coating film or by adding cushioning agent (Osei-Yeboah et al, 2017). The reported advantages of MUPs systems have generated significant interest in these dosage forms. Typically drug pellets are usually dispensed in capsules for the reason that no compression force is used and therefore the integrity of the pellets and the coating is likely to be maintained during processing. However, tableted systems provide a number of advantages over encapsulated systems (Augsburger and Hoag 2008). For instance, tablets are cheaper and simpler to produce. They are harder to tamper with than capsulated pellets. Moreover tablets are easier to swallow owning to their shape. They are also easier to break in half (for tablets with a breakage line) than it is to divide a capsule.

A notable requirement therefore exists to design robust pelletizing systems to withstand the forces applied during tablet compaction. This project is focused on developing techniques to predict and therefore control the quality of pelletized formulations produced in tablet form. In order to control the quality of pelletized systems, it is necessary to understand the processes involved in pellet production. The following section and figure below describes the method used in pellet manufacturing and characterization.

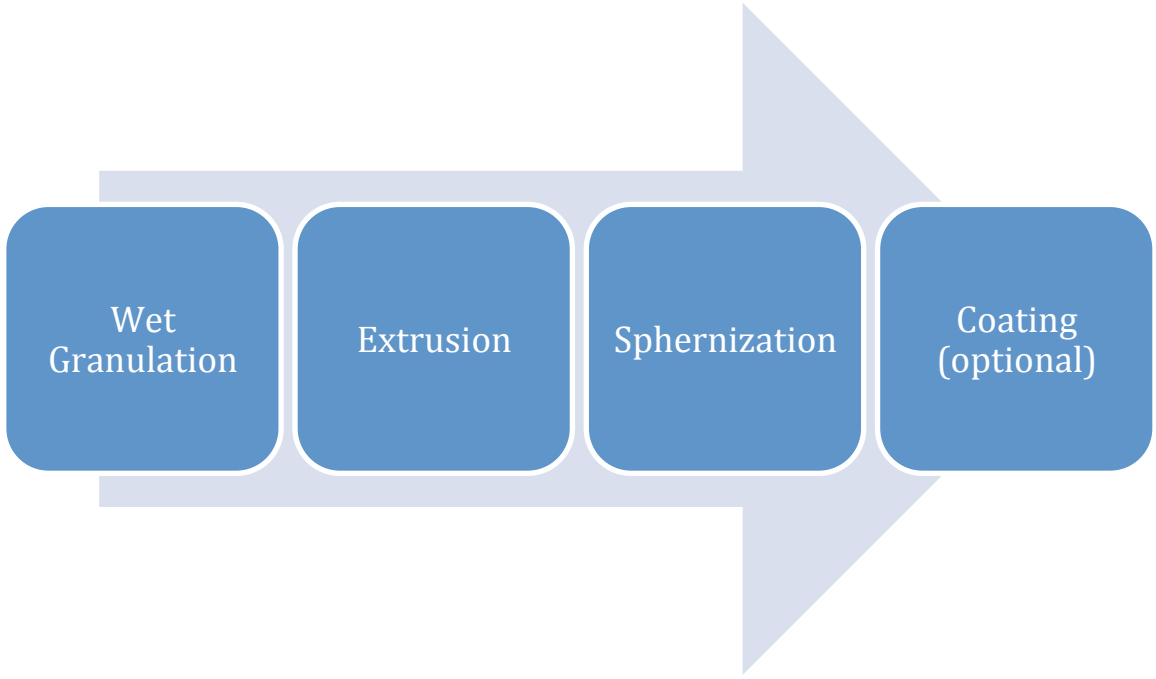

Figure 1-1: Summary of the pellets manufacturing process. Mixing is usually incorporated in the wet granulation process and the coating process is optional.

1.4 Wet granulation

Wet granulation is a commonly used process in pharmaceutical manufacturing and aims to increase particle size and density to improve the flowability and compressibility in downstream processes. In wet granulation, powder particles are agglomerated by adding wetting or granulating agents, whilst mixing and shearing is applied. Granule formation is achieved in few steps including, nucleation, growth, aggregation and breakage (as shown in Figure 1-2). (Kumar et al, 2014) (Yu et al, 2014). During the nucleation step, loose aggregates tend to form due to the capillary forces of the granulating liquid. The strength of granules then increases and granule growth continues by bonding and twinning until the granule reaches a firm size with strong bonds forming between particles. Large granules can break into pieces that recombine with themselves and with smaller granules to form increasingly strong granules. During the granulation process, some parameters must be optimized such as: particle size and size distribution of ingredients, the degree of agitation, binding agent selection (Wang et al, 2002) (Roy et al, 2010) (Wade et al, 2014)

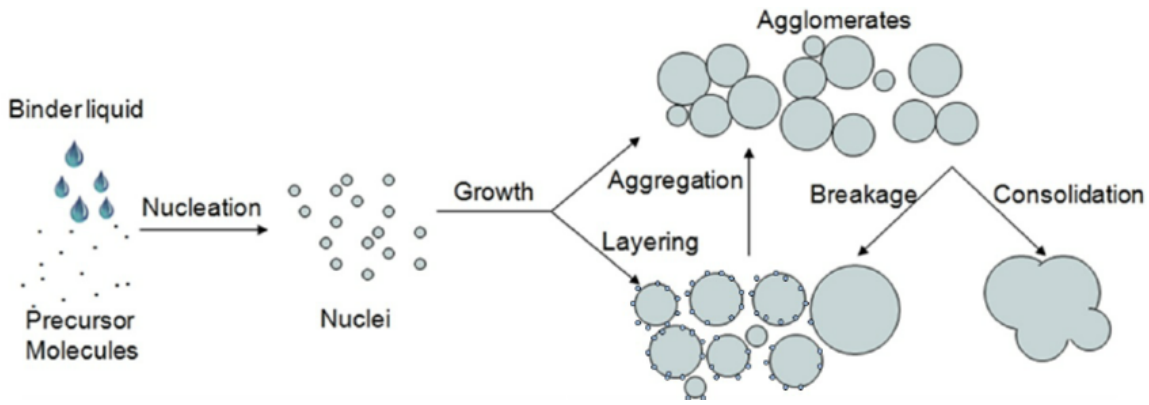

Figure 1-2: The steps of granule formation (Obtained from Kumar et al, 2014)

1.5 Extrusion-spheronization

Extrusion-spheronization process is commonly used in the pharmaceutical field to produce uniformed size pellets. It is ideal method for producing spherical granules with good uniformity in size, shape, density and a high level of drug loading up to 90% (Koester and Thommes, 2010). The extrusion-spheronization process starts with mixing of dry powders composed of drug and excipients to produce a homogeneous mixture, to which liquid binding agent, usually water, is then added. The wet blend is then passed through a perforated die, forming extrudate with spaghetti-like appearance. The purpose of these two steps is to essentially increase the density of the wet mass by reducing air gaps and plastic deformation of the solid binder (usually microcrystalline cellulose, MCC, or Kaolin). The density and diameter of the extrudates depends on the geometry of the extruder screen, type of binder used as well as the amount of added water (Feilden, Newton and Rowe,1993). Increasing the amount of water during the granulation step for example led to a reduction in the torque required to extrude the same mixture of MCC and lactose. Moreover, the type of extruder affected the size of the final pellets. This is attributed to the level of shear forces different types of extruders impart on the material (Feilden, Newton and Rowe,1993). Moreover the morphology of the additives could also impact the packing property of the extrudates and the final pellet sizes (Heng and Koo, 2001). The extrudate is then transferred to a spheronizer, which is composed of a stationary vertical cylinder having a grooved horizontal plate rotating at a variety of speeds. The mechanism of the spheronizer is based on the friction between the horizontal friction plate and

the extrudate. There are two types of the friction plate a radial geometry and a cross-hatched geometry plate (as shown in Figure 1-3). Radial geometry is found to impart higher shear force however it does not lend itself well to scaling up as the size of the grooves grows as the radius increases. On the other hand cross hatch geometry is more consistent (Muley et al, 2016) (Soh et al, 2013). The rounding of the extrudate into spheres is dependent on frictional forces. The forces are generated by particle-to-particle and particle-to-equipment interaction. During spheronization, strands of extrudate are subject to breakage to length roughly equal to their diameter forming short cylinders with rounded edges, followed by production of dumb-bells, ellipses, and finally spheroids (as shown in Figure 1-4a (Rowe, 1985). Another mechanism of formation was suggested by Baert and Remon indicating the possibility of twisting and breakage of the rounded cylinders leading to the formation of two smaller pellets (Figure 1-4b) (Vervaet, Baert and Remon, 1994). More recently, the mass transfer between the forming pellets was found to contribute to the overall spheronization process (Koester and Thommes 2010). The time for spheronization is about 5 to 15 min if all the process conditions are optimized. The majority of the deformation process takes place in the first two minutes before water evaporation reduce the plasticity of the wet mass (Rowe, 1985). The diameter of the produced pellets is based on the diameter of the perforated die (extruder) (Fielden et. al., 1993).

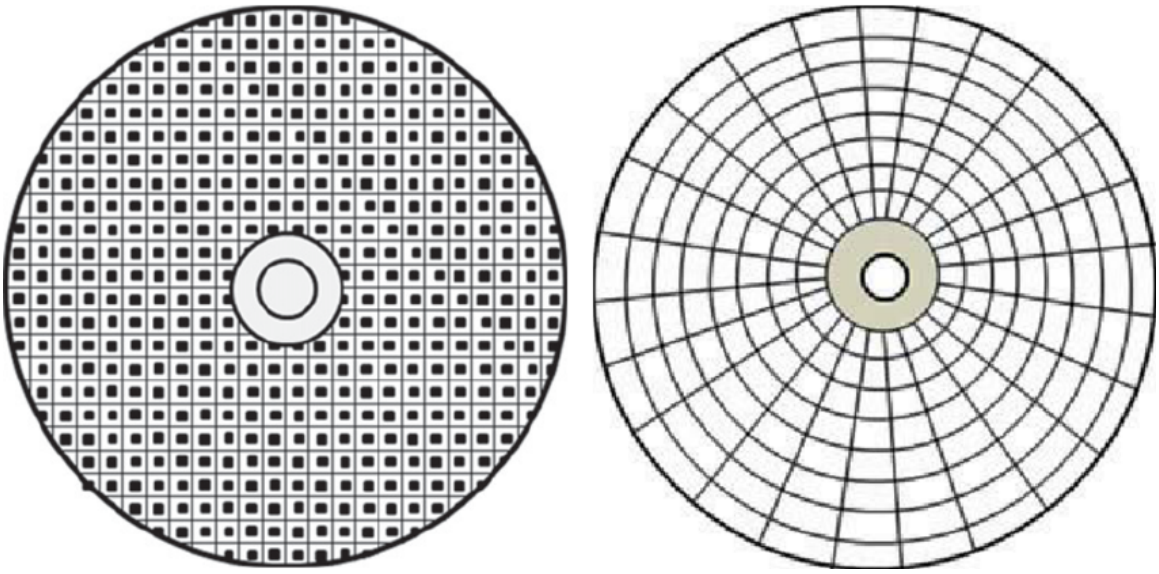

Figure 1-3: The geometrical design of friction plates used in spheronization. Left: The radial plate. Right: The Cross-hatched plate (obtained from Soh et al, 2013)

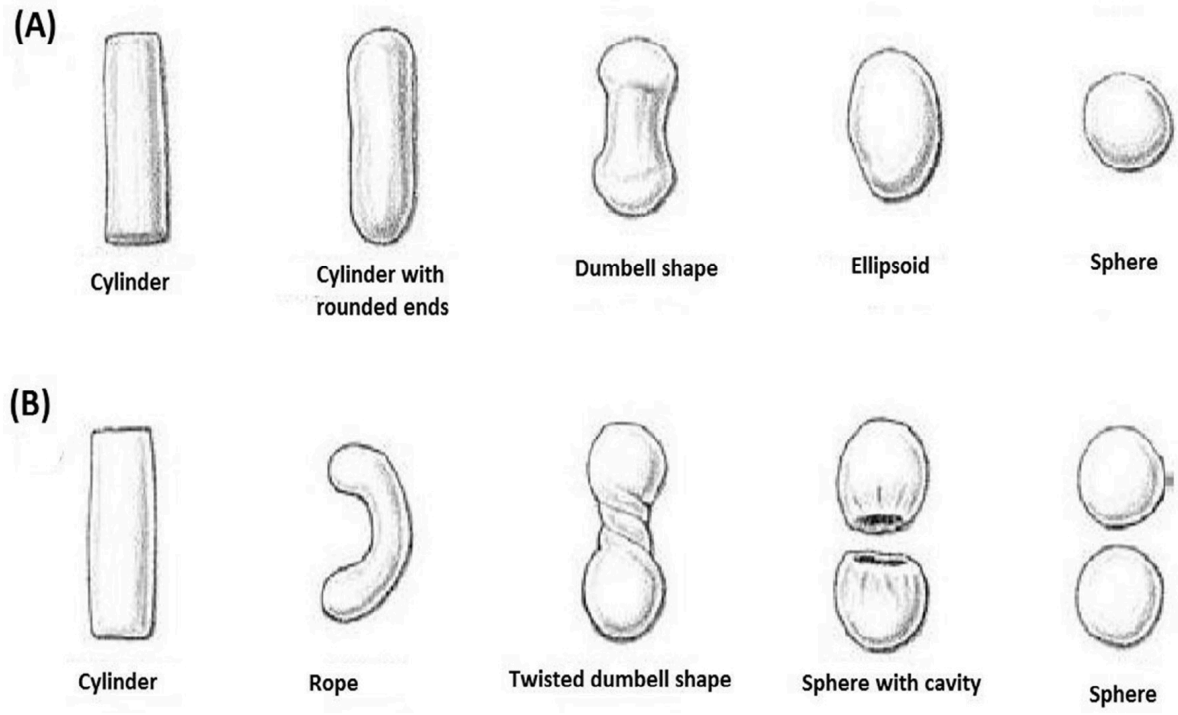

Figure 1-4a: The stages of pellets formation according to Rowe (A) and Baert (B) (obtained from Muley et al, 2016).

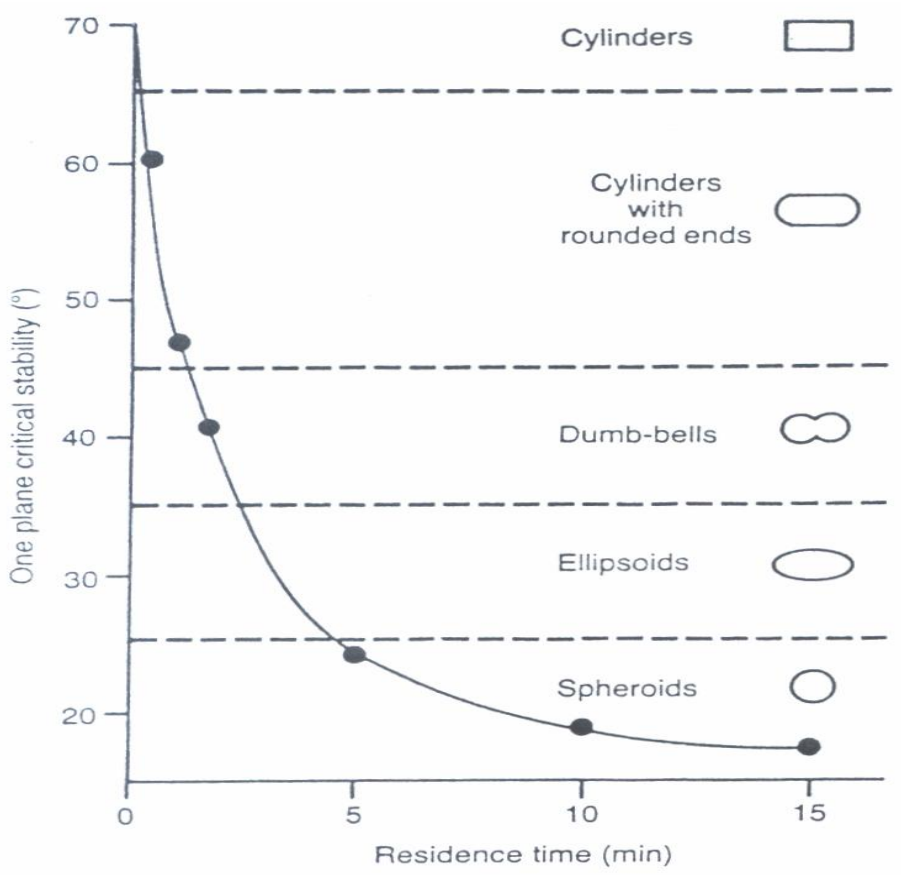

Figure 1-4b: The stages of pellet formation (obtained from Rowe, 1985)

The narrower the size distribution, the better quality of pellets owing to reduced potential for segregation. In addition to the shape of the spheronization plate, it was found that the speed of both the extrusion and spheronization as well as the speed and time spheronization affect the size and morphology of the pellets (Rowe 1985) (Muley et al, 2016)

During spheronization the combined effect of the heat, generated by friction, and the centrifugal force causes the moisture to migrate to the surface of the pellets. This could lead to sticking of the wet mass to the rotating blade or the side wall (Alderborn, 2013). Agglomeration of the pellets may also occur if excessive amount of water was used. An air extraction device can be fitted to

the roof of the spheronizer to prevent agglomeration. Alternatively, a temperature controlling jacket can also be placed around the spheronizing cylinder/drum. The aim of the above mentioned solutions is to accelerate the water evaporation on the surface of the pellets thus reducing the chance of agglomeration. Often dusting with a fine powder of microcrystalline cellulose can provide a practical solution to agglomeration (Fielden et al, 1993).

The efficiency of any friction plate design can often be compromised with the formulation of the material undergoing spheronization. If the material is sticky to the grooves of the friction plate can quickly become clogged with wet powder. This prevents further size reduction of the extrudate into uniform length leading to large size and shape distribution of the final product. This phenomenon can however be overcome using friction plates that have a Teflon edging. This reduces the amount of wet powder that adheres to the spheronizer wall adjacent to the friction plate and increases the upward motion of particles after they have collided with the spheronizer wall (Hicks and Freese, 1989) (Ghebre-Sellassie and Knoch, 1995).

Wet mass formulations used in extrusion spheronization have a tendency to be wetter than those used in wet granulation for tabletting and need not contain a conventional binder. The excipients used in extrusion-spheronization have fundamental influence on the spheroid formation, since they can attract the liquid phase by capillary force to increase granule strength, and improve cohesion. Some examples of these excipients include microcrystalline cellulose, kaolin, talc and bentonite. During the extrusion process, the binding agent tends to migrate to the surface of the wet blend where it plays a role as lubricant. However, good distribution of the binding

agent throughout the pellets is required to avoid excessive moisture content at the surface which can lead to agglomeration of pellets. Bentonite and microcrystalline cellulose are much easier to formulate as spheroids than kaolin and talc because they allow greater reabsorption of surface moisture into the extruder before spheronization. The extrudate must be adequately plastic so that it can be moulded into spheres without agglomeration (MacRitchie et al, 2002).

Microcrystalline cellulose is an ideal binder as it has a superior plastic deformability. However, it is typically more expensive and hence the interest in finding alternatives. Dukic-Ott et al, 2009, studied few suggested alternative to microcrystalline cellulose such as starch, chitosan, k-Carrageneenan, Pectinic acid, semi-synthetic polymers such as hydroxypropyl methylcellulose (HPMC) and hydroxyethyl cellulose (HEC), as well as, polyethylene oxide. It was found that none of the studied alternatives provided the same flexibility of MCC during extrusion-spheronization in terms of plasticity and dissolution performance

1.6 Advantages of Extrusion –Spheronization

In addition to the above-mentioned advantage of the production of dense rounded shape pellets with good flowability, the process of pellitization offers many more advantages. For example, the same process could be tweaked to produce consistent pellets with a diameter of any value between 0.5-15mm. Moreover, the elimination of intermediate drying steps (compared to wet granulation tabletting process) reduces the risk of producing dust

(flammable dust of cellulose excipients and potent drug dust) (Rowe 1985) (Fielden et. al., 1993).

1.7 Pellets characterization and evaluation

1.8 Film coating

After the production of pellets, they are often film coated. . In this process, a thin polymer layer is applied to the surface of the solid dosage form such as tablets or pellets. The thickness of a film usually ranges from 10 to 100 μm. The thickness and integrity of the coating film are very significant especially for functional coating, as this will affect the drug release and the tendency of film defect (Knop et al, 2013) (Porter, 1995).

1.8.1 Reasons for coating:

The mains reasons for coating of pellets/tablets in pharmaceutical manufacturing are:

- To mask the offending taste of some medicine (mainly those of weak alkaline nature).
- To improve the physical appearance of the final dosage form and to facilitate drug identification. (Siepmann et al, 2013)
- To improve the stability of medicine by protecting the drug from surrounded environment such as moisture, light.
- To improve the durability of tablets to withstand the packaging and transportation
- To modify the drug release and to control the delivery of the drug to the expected site (Maroni et al, 2013)

1.9 Film coating materials

Most of film coating formulations have the following ingredients:

- Polymers
- Plasticizers
- Solvents/vehicles

Other excipients could be added such as surfactants, opacifiers and colourants (Knop et al, 2013)

1.9.1 Polymers

Polymers are the backbone of film coating formulation. They can be used alone or with other polymer if it is required. A polymer is composed of chains of repeated units (called monomers) (Karki et al, 2016). Polymers can be classified based on their origin into:

- Natural polymers such as starch and proteins.
- Semisynthetic polymers such as HPMC, MC, HEC
- Synthetic polymers such as PEG, PVA, PVP

In addition, polymer can be classified based on the structure as the following:

- Linear polymers: Each chain represent one continuous line with no branches or forks.
- Branched chain polymers: in which the chain have single or multiple branches along the main backbone.
- Cross-linked polymers: The chains are branched and they are chemically interlinked to each other restricting the overall free movement of the chains (Aulton, 1984)

Most the linear and lightly branched polymers are thermoplastic in nature. This means they soften gradually upon heating and gain their rigidity back once cooled.

Furthermore, polymers can be classified based on their internal morphology into:

- Amorphous polymers
- Semi-crystalline polymers (Dyson, 1998)

1.9.2 Plasticizers

Plasticizers are low molecular weight polymers that are capable of modifying the physical properties of film coating polymer. Typically, plasticizers improve the flexibility and reduce the Tg of the coating polymer. They achieve this by interacting with the polymer chain and increasing the free volume between the chains. This increase the molecular mobility and reduces the mechanical strength of the polymer. (Bodmeier and Paeratakuel, 1997). The hydrophilicity of the plasticizer affects the properties of the final film such as water uptake and drug release (Locomte et al., 2004). Table 1-1 provide a list of examples of such plasticizers. Moreover, the strength of the interaction between the polymer and the plasticizer can also determine its impact on the mechanical properties of the film which consequently affect coalescence and drug release (Fukui, 2001). In addition plasticizers can also alter other coat properties such as adhesion (Shan-Yang et al., 2000).

When selecting a plasticizer there are many important factors to consider including efficiency, compatibility, and permanence, (Portor, et al, 2017).

Hydrophilic plasticizers	Hydrophobic plasticizers
Glycerin Polyethylene Glycols Polyethylene Glycol Monomethyl Ether Propylene Glycol Sorbitol Sorbitan Solution	Acetyl Tributyl Citrate Acetyl Triethyl Citrate Castor Oil Diacetylated Monoglycerides Dibutyl Sebacate Diethyl Phthalate Triacetin Tributyl Citrate Triethyl Citrate

Table 1-1. List of plasticizers declared in USP 35-NF 30

1.9.3 Solvents/vehicles

Solvents are the materials that can dissolve or carry other substance without affecting the nature of both the solvent or the carried substance. Solvents can be water or organic solvent such as alcohol, ketones, esters or chlorinated hydrocarbons (Beaugendre et al, 2017)

1.10 Ethyl cellulose as a film coating polymer

In this research work, ethylcellulose (EC) was used as a coating polymer. It is a semisynthetic cellulose polymer. Its chemical structure composed of

chains of anhydroglucose units linked by oxygen bridges (as shown in figure 1-5). It is commonly used coating polymer in the pharmaceutical industry because of its safety profile. Also, EC is water insoluble polymer and widely used to control the drug release where the release occurs through permeation into the coating film (Lai et al, 2010).

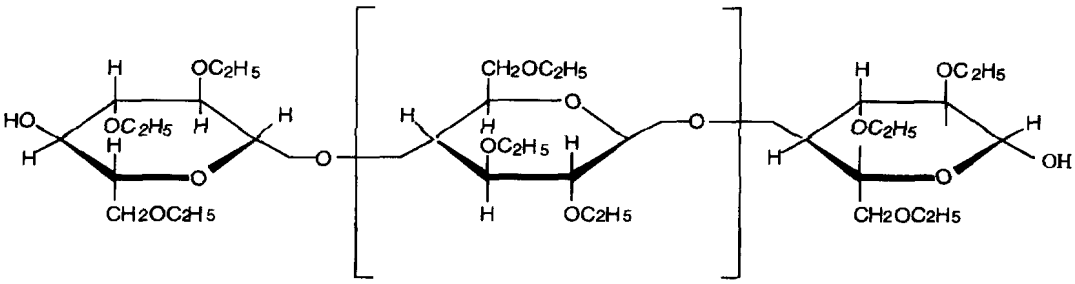

Figure 1-5. Chemical structure of Ethylcellulose (Hyppola et al, 1996)

1.10.1 Mechanism of film formation

Film coating is a process in which a polymeric coating solution is sprayed as droplets on a substrate's surface. The coating solution composed of a coating polymer which is either dissolved or suspended in a suitable solvent. The droplet impact the substrate and spread on its surface. The drying of the solvent causes the polymer to concentrate, entangle and form a gel. The drying continues causing the gel to condense into a film. In addition to the evaporation, the film formation requires coalescence of droplet and subsequent integrating of the coating polymer into a coherent dense film shown in figures 1-6a and 1-6b. (Felton, 2013).

During the coating process the degree of spreadability of the droplet on the substrate is based on the surface tension. Moreover, it is based on the nature of both the coating solution and the substrate surface such as the roughness, and the porosity. Moreover, processing condition for example atomized air pressure, the temperature of inlet air, the location of the spray gun and the distance between the air gun and the substrate (Felton, 2013) (Porter, 2012) (Bruce et al., 2011)

During the evaporation process of the coating film, the size of the substrate is relatively constant however the solvent start to evaporate this will cause the film to shrink as the capillary force forcess the film to be pulled together. When the film is wet, it can dissipate this energy (stress), however as the film dry it becomes more elastic and the stress builds up inside the film (internal stress). There are some problems that can be seen in tablet coating such as cracking, peeling and logo bridging because of the internal stress inside the coating polymer. Since the nature of the coating film is viscoelastic the film could dissipate the internal stress over shelf life however if the internal stress is higher than the tensile strength of the polymer then cracking takes place. Meanwhile if the internal stress is higher than the adhesion force of the film to the tablet the film will be detach from the surface of the tablet leading to bridging or peeling (Felton et al 1999) (Felton, 2013)

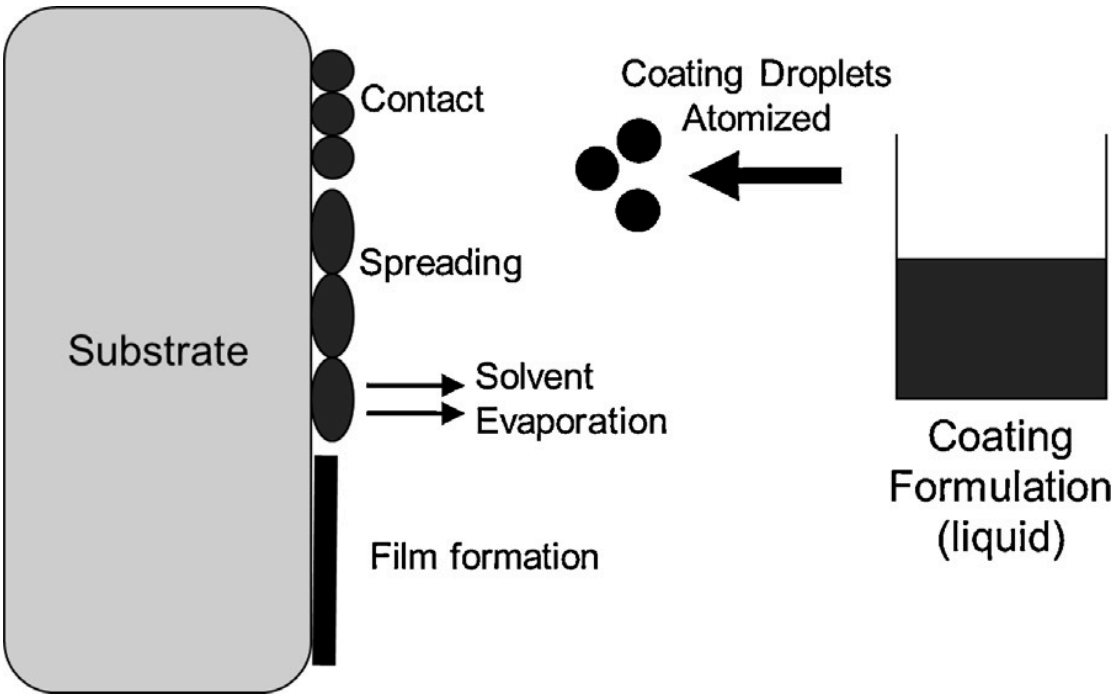

Figure 1-6a. The steps of film formation (Felton, 2013)

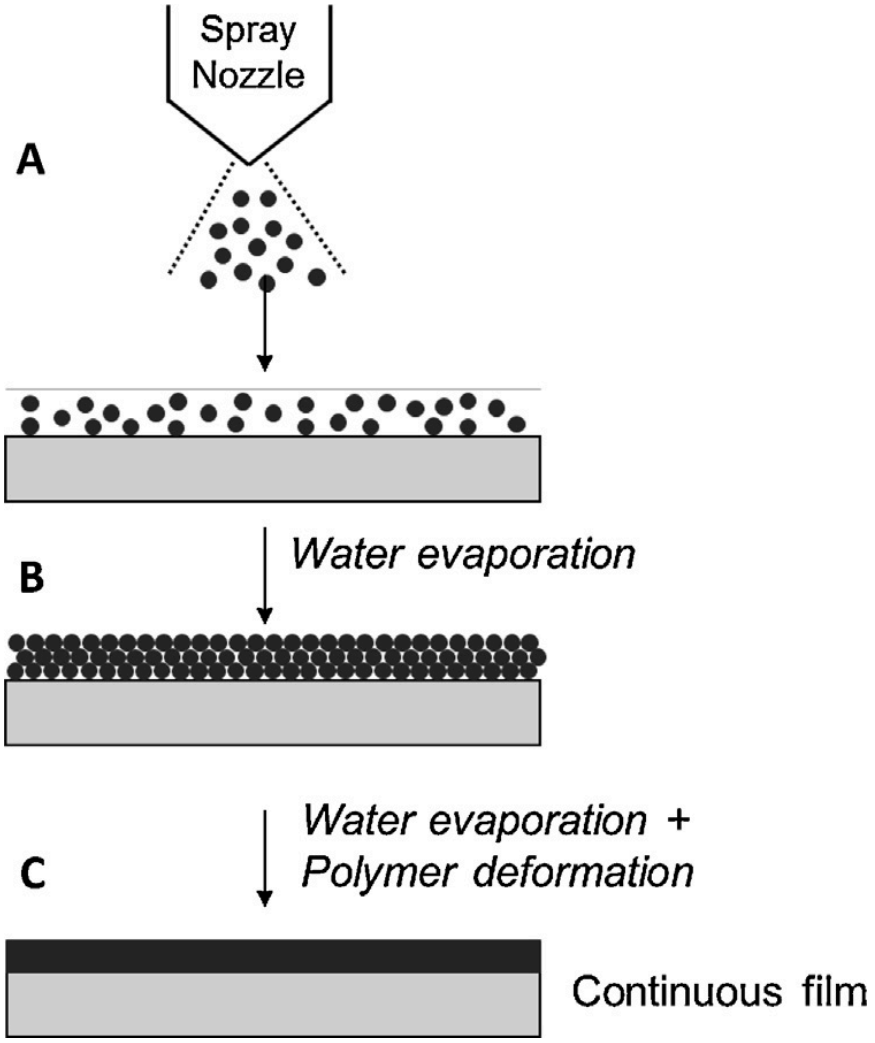

Figure 1-6b The steps of film formation (Felton, 2013)

It is essential to understand the rheological behaviour of the polymer under coating as well as compression conditions. This study was carried out using organic-based solution of ethyl cellulose. Therefore rheological properties are not as critical for film formation as it is in the case when using aqueous suspension. However film quality and release profile are all influenced by the rheological properties of the film at various temperatures, humidity and shear force regimes. Moreover if the coated pellets are to be compressed it is

essential to understand the behaviour of the film under the compression conditions (compression force, speed and dwell time).

Inside the polymeric materials there are number of interactions between the chains. These inter-chain interactions control the rotation and ability of polymer chains. As a result of that, the dynamics of polymers are mainly affected by the strength and number of these internal interactions. Changes in the arrangement of the polymeric chains can occur only if there exists sufficient energy to break the chain arrangement. This is known as the energy barrier of the transition between the two conformational states and is usually overcome by raising the temperature of the sample. Furthermore, the rate of transition is determined by the energy provided. The greater the shear rate, the higher the energy required to achieve a comparable relaxation time (Isreb, 2011). Viscoelasic materials behave as solid or liquid depending on the temperature and/or the shear rate. Changing the shear rate can change the behaviour of the material to liquid or solid state (Mezger, 2006)

Generally, a material can change from one physical status to another based on the gained energy. i.e., when the gained energy in that material is higher than its energy barrier. Both the mechanical properties and conformational status of the material transforms from one physical state to another by changing either the applied strain or its temperature. There are five different states as here described (Mezger, 2006) (Isreb, 2011):

1. Glassy state: in which the polymeric network is almost solid, in this case the material behaves like elastic material. As it is shown on figure 1-6 (zone

A), G' is significantly higher than G". This makes it hard for the material to dissipate energy as a result of the restricted movement of the polymer chains.

2. Glass to rubber transition: in which the polymeric network is strong, although the branches are easy to be deformed. The material in this case is viscoelastic. (Shown as region B at figure 1-7)

3. Rubber state: in which the polymeric network is weak. In which the elastic component is more pronounced than the viscous component (Shown as region C at figure 1-7)

4. Rubber/liquid transition: in which the polymer shows equal viscous and elastic behaviour.

5. Viscoelastic liquid: in which the polymeric network can be represented by a simple Maxwell model. The viscous component is dominant, and stress is dissipated.

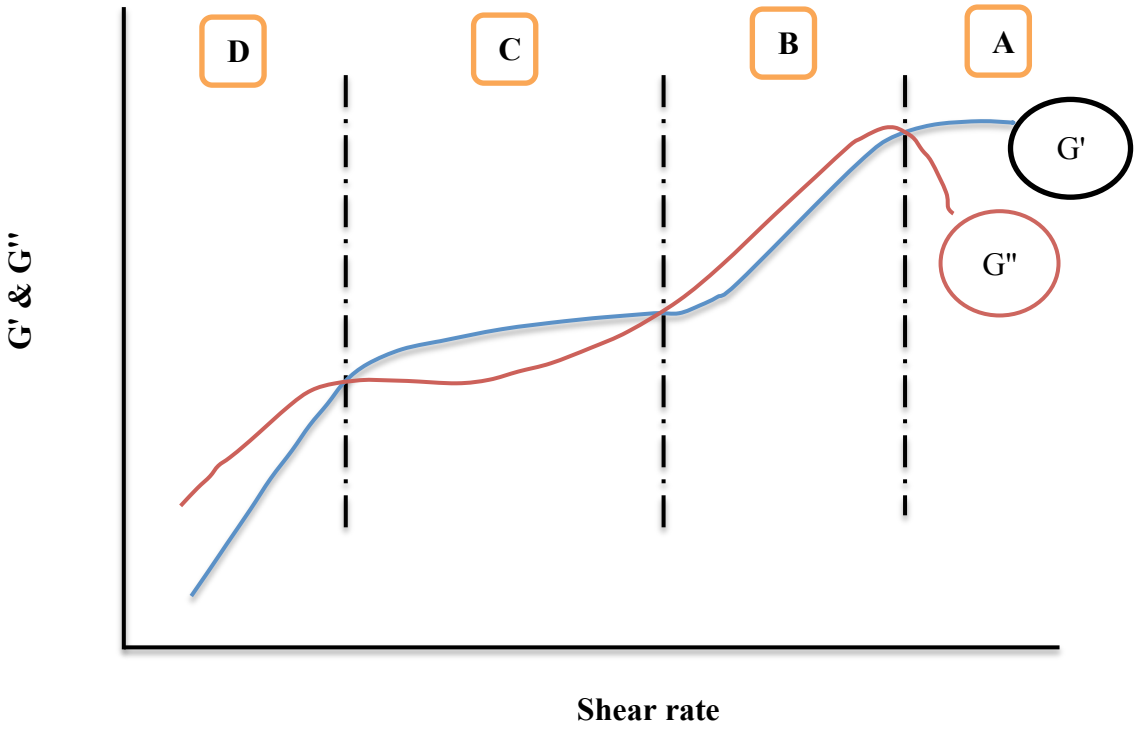

Figure 1-7 Ideal dynamic frequency sweep test of a viscoelastic polymer. A; Glass state, B: Glass to rubber transition, C: Rubber state, D: Viscoelastic liquid (adapted with modification from Isreb, 2011)

1.10.2 Tabletting of coated pellets

During the tabletting of coated pellets it is crucial that the pellets are capable of accommodation the applied compression force without any damage. Generally, the pellet core is the main component involved in the compression of pellets. The elasticity of the pellet core is an important property by which the pellets can resist changes in shape and deformation during compression. Typically, pellets should deform and recover after compression without damage to the coating. In addition, excipients are added to absorb the applied pressure, deform and form the tablet while preventing the pellets

from crushing into each other reducing the damage to the coat. These excipients are commonly called cushing agents (Cepsi et al, 2007).

Béchard et al found that the size of the coated pellets can influence the compaction properties and drug release from the compacted pellets. When small and large pellets of chlorpheniramine were coated at the same level,the small pellets were more brittle than large pellets. This was because of the reduced coating film thickness due to the greater surface area of the small pellets (Béchard et al, 1992) (Choudhary et al, 2013)

Debunne et al evaluated the influence of size on the compression of coated pellets. It was found that pellets with size from 0.3 to 0.5 mm formed more bonds during compaction than larger pellet (0.8-1.2 mm) due to their larger surface area, leading to improvement in the mechanical strength of the tablet. Moreover, the release rate was enhanced by reducing the pellet size from 0.8-1.2 mm to 0.3-0.5 mm as the surface area increased (Debunne et al, 2004).

Typically, the cushioning agents form a significant proportion of the final tablet weight up to 60% w/w. They are usually a mixture of a compressible polymer (MCC) and fillers such as lactose (Patel et al, 2018). This preserve the functional coat of the pellets and maintain the release profile. However it causes the problems of segregation due to the large difference in density between the dense pellets and the powdery excipients. In addition the use of large percentage of cushioning agents reduces the maximum drug loading capacity of the final tablets. Therefore alternative strategies were investigated including adding extra coating layer of a heavily plasticized coat

to provide the binding effect without compromising the functional coat (Osie-Yeboah et al, 2017). The malleable top coat provides the three dimensional bonding network to keep the integrity of the tablets (Sun, 2016). While this was claimed to be a universal strategy for the manufacturing of MUPs, it is still worth noting that the addition of another thick coating layer would slow the production process. Moreover, the possibility of the migration of the plasticizer from the top coat to the functional coat and its impact on the drug release over the shelf life was not investigated. Furthermore, The amount of plasticizer used was not selected by a systematic approach but rather by trial and error.

Layering the top surface of the pellets with cushioning agents was also proposed to alleviate the segregation issue (Hosseini et al, 2013). However, the high proportion of excipients was still an issue.

Therefore, it seems to be that there is a need to develop a quality-by-design approach to assess the performance of the coat and identify its viscoelastic behaviour under compression stress. This approach would eliminate the need for an extra coating layer and would identify the amount of plasticizer required to achieve optimum compression without loss of functionality.

The next part of the literature review therefore will focus on understanding the viscoelastic behaviour of polymers in order to employ this field in the study of the properties of the film under coating as well as compression conditions.

1.11 Mechanical, rheological and viscoelasticity of the coating film

In order to be able to assess the performance of the film during coating and compression, it is essential to understand the chain dynamics and the flow of the polymer under various temperatures and shear regimes. It has been long established that the behaviour of the polymeric chains during film coating directly affect the coating film formation and its quality. There are different film coating defects for instance peeling, logo bridging, and spray drying that are deep-rooted in the viscoelastic properties of the film coating formulation. For instance when the internal stress of the coating film is larger than the tensile strength, the coating film tends to crack or peel. While, logo bridging occurs when the internal stress inside the film is higher than the adhesion force (Rowe, 1978). Therefore, understanding and evaluating the rheological characteristics is very significant in order to avoid difficulties during the coating.

The effect of compression has not been thoroughly investigated in film coating, Nevertheless, the performance of plastic deformation has been extensively studied in the field of granulation and tabletting (Bacher et al, 2008).

1.12 Viscoelastic terminology

In order to discuss viscoelastic bahviour of polymers, it is imperative to start by defining the meaning of the basic terms (Mezger, 2016):

1.12.1 Stress

It can be defined as an applied force per unit area. That force can be tensile, compression or shear force. The S.I. unit of the shear stress is (Pa), (“Pascal”)

1.12.2 Strain

It is a measure of the deformation of the polymer chains due to the applied force. It is a dimensionless quantity as it is presented as a fraction of the change in the dimension that is under stress. The terms strain and deformation are very similar and many people use both terms interchangeably (Larson, 1999)

1.12.3 Storage modulus (Elastic, G’):

It is the ability of a material to be deformed elastically (non-permanently) under an applied stress. In other words, when a material is subjected to a stress, the material will store the energy and once the applied force is removed, the material will release that energy to return to its original shape. The storage modulus of a material is described as the slope of its stress-strain curve in the linear viscoelastic deformation zone. It can be described as in the following equation:

G'= Stress/Strain (Equation 1-1)

Where G' is the elastic modulus

1.12.4 Loss modulus (viscous modulus, G"):

It refers to the ability of the material to dissipate the energy of the applied force as a friction heat. Loss modulus represents the viscous part of the material and is responsible for the plastic effect of polymers. i.e. the permanent deformation under the applied pressure.

1.12.5 Tan Delta:

It can be defined as the tangent of the phase angle δ between the stress and strain during oscillatory test. Tan delta can be used to characterize the modulus of the material; it can be obtained from the ratio of loss modulus to storage modulus. It can be calculated by the following equation (Isreb, 2011) (Mezger. 2006):

Tan delta= G"/ G' (Equation 1-2)

Generally, tan delta is used to evaluate the balance between the viscous and elastic portions. When the value of tan delta (δ) is more than 1, which means the material is more plastic, while tan delta (δ) below 1, which means the material, has more elastic components.

1.12.6 Strain rate

It is the rate of the change in strain with time. The unit of the shear rate is reciprocal seconds (s^{-1}). It can be referred to as shear rate

when the strain is caused by two parallel plates causing changes in the velocity of two adjacent layers of the polymer..

1.12.7 Viscoelasticity

It is the phenomena at which a material exhibits behaviour in between elastic and viscous materials.

1.12.8 Complex viscosity

It defines the flow resistance of the sample in the structured state, originating as viscous or elastic flow resistance to the oscillating movement, usually measured in Pascal second (Pa.S) (Isreb, 2011)

1.12.9 Newtonian fluid

When curve of the stress v.s strain is linear and passes through the origin, the fluid called Newtonian. (i.e. water is a good example for the Newtonian as the shear stress does not change the viscosity).

1.12.10 Non-Newtonian

The viscosity of the non-Newtonian fluids is dependent on the stress or shear rate

1.12.11 Shear thinning

It is a phenomenon in which the viscosity of a fluid decreases with an increase in the shear rate. Pseudo plastic is a synonym for shear thinning

1.12.12 Hooke's law

In 1675 Robert Hooke studied the linear relationship between the stress and strain. The linear relationship commonly referred to as Hooke's law. It expressed the relationship between force and displacement as the following:

$$F = - kx \qquad \text{(Equation 1-3)}$$

Where

F is the applied force

k is the spring constant (each spring has different strength or k)

x is the displacement (refers to how far the spring was forced or pushed)

Also, it can be expressed as the following:

$$\sigma = E\varepsilon, \qquad \text{(Equation 1-4)}$$

Where δ is the applied stress, E is the Elastic modulus, and it is named the Young's modulus in tensile testing. Young's modulus is a good guidance to the elasticity of the material. By increasing the value of the Young modulus, the elasticity increases (Mezger, 2006)

When a stress is applied on an elastic material, the interactive forces between the atoms and molecules of the deformed material become strong. If the linear-elastic range is exceeded, the relation between stress and strain becomes non-linear and the deformed materials tend to break (Mezger, 2006).

1.13 Elastic, plastic and viscoelastic behaviours

Materials can be divided into three different types based on their response to the applied force as the following:

1.13.1 Plastic materials

Plasticity is the term that defines the deformation of material due to an applied stress, and this deformation in not recoverable. In physics, plasticity can be defined as the tendency of a material to undergo permanent deformation under load. This behaviour is characteristic of many polymers and metal alloys. Furthermore, it does not include glasses and other ceramic materials. The relationship between stress and deformation is nonlinear.

1.13.2 Elastic materials

Elasticity can be defines as the ability of a deformed material, due to applied force (stress), to restore its original shape when the applied stress is removed. A material with this feature is called Elastic material. The elastic deformation behaviour can be described by Hooke's law as discussed previously on 1.14.12

1.13.3 Viscoelastic materials

Materials that exhibit both viscous and elastic behaviour simultaneously when undergoing deformation are called viscoelastic materials. Since it has viscous and elastic characteristics, it follows Newton's law and Hook's law respectively. When a stress is applied on a viscoelastic polymer, the material starts to set its molecular arrangement which is called Creep. Most of the pharmaceuticals materials are viscoelastic. The viscoelasticity can be studied by using Dynamic Mechanical Analysis, where an oscillatory stress is applied on a material and the strain is measured. The elastic and viscous portions are called storage modulus (G') and loss

modulus (G") respectively. In this case the relation between the oscillating stress and strain (deformation) can be expressed by the following equation:

$$G = G' + iG'' \qquad \text{(Equation 1-5)}$$

Where: G = the complex modulus

G' = the storage modulus

G" = the loss modulus

i = the imaginary number = $\sqrt{-1}$

1.14 Aim and Objectives:

Multiple unit pellet systems offer the advantage and the flexibility of creating multiple mini drug reservoirs that can be engineered to deliver a tailored release profile. In order to avoid coat rupture, cushioning agents are usually added in significant proportion. This causes many drawbacks including limited drug loading and segregation during tabletting. So far, the alternative strategies focused on providing extra cushioning to protect the functional coat rather than trying to understand the behaviour of the coat itself under compression conditions. The aim of this study is to investigate the feasibility of establishing a comprehensive profiling of the viscoelastic behaviour of the polymer to predict the performance of film coating in compressed coated pellets without using cushioning agents or extra coating material. The objectives of the study are:

1. To investigate the feasibility of reconciling DMA data from tensile clamp with those obtained with parallel plate shear rheometer to build a complete rheological profile of ethyl cellulose under various compression regimes.
2. To investigate the influential parameters affecting the film performance during the compression process using experimental design approach. The parameters investigated are compression force, dwell time and coating level.
3. To investigate the effect of two plasticizers (PEG400, TEC) on the thermal and mechanical properties of ethyl cellulose and its overall viscoelastic behaviour
4. To evaluate the feasilibility of using the rheological and mechanical properties of the polymer to explain and predict its performance during coating and compression processes.

Chapter 2
Materials and Methods

2. Chapter 2: Materials and methods

2.1 Materials

The materials used in this research work were the following:

Theophylline, anhydrous, minimum 99%, Sigma, batch no. 048K0709

Microcrystalline cellulose (Avicel) PH101, batch No. 6622C

Lactose, SuperTab® 21 AN, lot no. 10385468 from DMV-Fonterra Excipient GMBH & Co.

Ethylcellulose (Ethocel standard 10 premium) was donated from Colorcon®, batch no. DT217211.

Triethyl citrate, 99% from purchased Sigma-Aldrich®, batch no. 02216BH.

PEG 400 from Sigma®, Germany, batch no. 39H 0110, it was used as plasticizer

Ethanol 99.9% was used as organic solvent.

Precisa 30100DG-FR SCS balance.

Hobart mixer model no. SEF25/92 was used for dry mixing and wet granulation processes.

Alexanderwerk commercial cylinder extruder.

Caleva spheronizer with cross-hatched frictional plate

Qualivac vacuum oven from LTE ScientificnLtd., was used for drying.

2.2 Methods

2.2.1 Pellets production

Pellets were prepared by weighing 250 g of each lactose and Avicel^{TM}. Initially both components were dry mixed together in a Hobart planetary mixer for 5 min at lowest speed level. Water was used as wetting agent and added in the ratio of (1:1:1.1 w/w) Lactose: Avicel: Water respectively, and was mixed for another 10 min to ensure homogenous wetness of the batch.. At this stage, the wet mass was taken and was left in a sealed container for 12 hours at room temperature to ensure homogenous distribution of moisture in the wet mass. The Alexanderwerk extruder set with 1 mm die was used to extrude the wet mass at a speed mark 3. The extrudates were collected and spheronized using the Caleva spheronizer with a 15 inch cross-hatched plate and the spheronization speed was 500 rpm. After 30 min of spheronization, the collected batch was taken and distributed on flat trays, left to dry at room temperature for 24h and then dried in a static oven at 60 C$^{\circ}$ for another 24 hours (MacRitchie, 2002)

2.3 Characterisation of Pellets

2.3.1 Size analysis of prepared pellets

The dried pellets were sieved through a set of British Standard Sieves. In this research work, different sieves fractions were obtained and pellets with size from 0.85 to 1.2 mm were collected and mixed for 10 min using a tumbler mixer. (Akhgari et al, 2011). The reason of taking this narrow size limit is to avoid segregation problems that may appear during handling the pellets such as during coating and filling the die during tabletting. Pellets with a wider

range of particle size would end up with various coating level due to the difference in surface area. Moreover, small pellets would have different packing order to larger pellets making tablet weight inconsistent.

2.3.2 Preparation of free film

Free cast films were prepared using ethylcellulose as a coating polymer. Triethyl citrate (TEC) and polyethylene glycol (PEG) 400 were used individually as a plasticiser. The level of each plasticiser was specified in each individual case (0, 5, 10, 20, and 30 w/w). Acetate sheets, were used to cover the petri-dishes to make peeling the dried casting film more easier. Initial trials were conducted to determine the suitable concentration of coating polymer, and 10% w/w was found as the most appropriate concentration. When high concentrations 20 and 30% w/w, of coating polymers were evaluated, both solublisation and viscosity problems were faced, as it was hard to solubilize and even after making a coating solution with 20 and 30% concentrations, it was hard to spray the coating solution because of its high viscosity.

10% w/w of ethylcellulose was added slowly to the solvent and mixed by a magnetic stirrer within a beaker for 3 hours and then the plasticizer was added and further mixed for 30 min. Therefore, the stirring was continued for 30 min, the mixture was then centrifuged at 3000 rpm for 10 minutes to remove the air bubbles within the polymeric coating solution. 50 ml of the polymeric solution was then poured over an acetate sheet placed on levelled glass Petri-dishes of 14 cm in diameter. The films were left to dry in a cabinet

box for 72 hours, at room temperature and then peeled off the mould using a spatula and scalpel (Isreb, 2011) (Hyppölä et al, 1996).

All the films were stored in sealed bags at the room temperature. Free film samples were characterized by Scanning Electron Microscopic (SEM), Thermogravimetric analysis (TGA), Differential Scanning Calorimetry (DSC), and Dynamic Mechanical Analysis (DMA).

2.3.3 Scanning Electron Microscopy (SEM)

Using a SEM (SEM FEI QUANTA 400, Oxford instruments, INCAx-sight), with aluminium stubs and carbon tabs (12 mm Dia, FK 100), samples of free films were fixed on a stub by using a carbon tape. The samples were coated with gold dust (EMITECH K550, the gold thickness was 15 nm).

2.3.4 TGA analysis

Thermogravimetric Analysis (TGA) is a laboratory technique that measures the weight changing of a material as a function of temperature or isothermally as a function of time under the same condition to measure the loss of volatile materials and identify the degradation temperature. In this research work the TGA was used to determine the temperature range that will be used in DSC, which is necessary to avoid sample decomposition during DSC trials. TGA (Q 500 TA Instruments) was used to evaluate the moisture content in each sample. The samples were scanned using a TGA and standard platinum pan. Samples (weighing 6 ±1 mg) were measured at a scan rate of 10 $^{\circ}$C/min under nitrogen gas atmosphere. The temperature of TGA furnace was calibrated using the Curie point temperature of nickel metal. The sample was scanned from room temperature to 300 °C on ramp

heating mode and the gas flow was 20 ml/min. A cork borer (size 2) was used to cut small homogeneous discs with flat surfaces (to ensure an equal exposure to heat) that fit into the aluminium pans. All the experiments were repeated three times and analysed by using Universal analysis 2000 version 4.3A. (Lai et al, 2010)

2.3.5 Differential Scanning Calorimetry (DSC)

DSC technique measures both the absorbed and released temperature by a material when it is heated or cooled, showing quantitative and qualitative data on endothermic and exothermic reactions. It is widely used in pharmaceutical research for its capability to measure melting temperature, heat fusion, glass transition temperature, crystalline phase transition, oxidative/thermal stability. The theory of the DSC is based on measuring the difference in the amount of energy (heat) required to raise the temperature of a sample and reference as a function. Both the sample and reference are upheld at the same temperature during the experiment. During the DSC studies there are few terms that have to be understood such as: **A calorimeter** evaluates the absorbed and released heat of a sample**. A differential calorimeter** evaluates the heat of a sample relative to a reference**. A differential scanning calorimeter** measures the absorbed and released heat of a sample, measured the heat of a sample relative to a reference, and heats the sample with a linear temperature ramp**. Exothermic** heat flows out the sample**. Endothermic** heat flows into the sample, in another meaning adding a heat or energy to a subject. The transition glass and melting both are good examples for the endothermic. **A glass transition temperature (Tg):** it is the temperature at which the

material changes its behaviour from Glassy (hard and brittle) to rubbery (flexible and elastic). The term Tg is only used for amorphous (non-crystalline) materials. Amorphous materials are predominantly either rubbers or glasses. **Amorphous materials:** the materials that do not have their atoms or molecules arranged on a lattice that repeats periodically in space. (Haines, 1995)

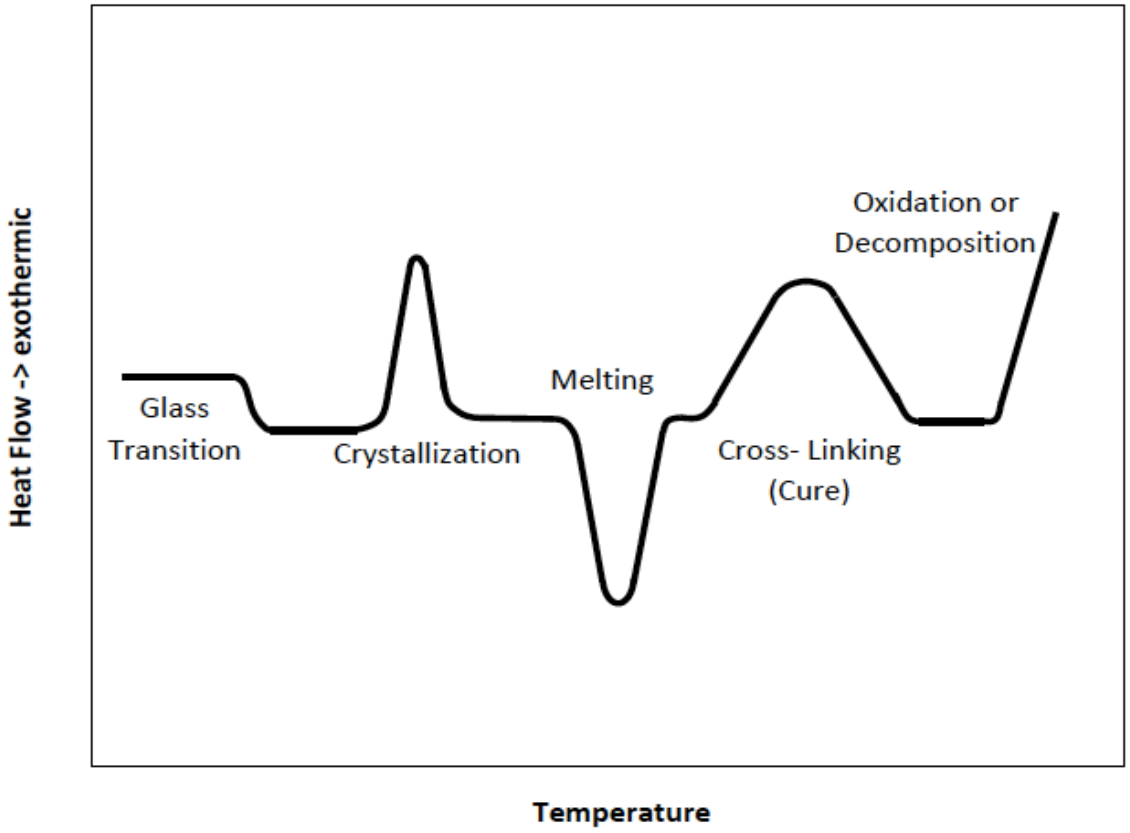

Figure 2-1: Typical DSC transitions (adapted with modification from Haines, 1995)

During analysis of semi crystalline polymer which includes amorphous and crystalline

portions, there are two transitions can be seen, the melting and the glass transition. The melting reveals the transition of the crystalline portion, and the glass transition reflects the change in the amorphous portion of the same polymer (as shown above on figure 2-1).

In this research work, DSC (TA Q 2000 TA Instruments) with refrigerated system was used. All the samples were subjected to a heat/ cool/ heat cycle at a rate of 10 C/min and were scanned using standard aluminium DSC lid and pan. An empty pan was used as a reference. Samples weighing 8±2 mg were placed into the pan and lid was pin-holed (to allow evaporated moisture to escape and not affect the subsequent cooling and second heating cycle) was used to cover the pan. The DSC was calibrated using the melting point of reference indium sample. Each sample was scanned from room temperature to appropriate temperature determined from the degradation temperature from the TGA, and cooled to – 60° C and reheated up to the same temperature. The glass transition was measured from the second run to eliminate the effect of the thermal history and themoisture content of the material. The obtained results were analysed using the software “Universal analysis 2000 version 4.3 A” and each experiment was repeated using 3 samples to ensure consistency (Lai et al, 2010)

2.3.6 DMA

Dynamical Mechanical Analysis (DMA) is a thermal analysis technique to measures the mechanical properties of materials as they deformed when mechanical force/ stress is applied. Simply the DMA is an analytical technique in which an oscillating stress is applied to a sample and the resultant strain measured as functions of both oscillatory frequency and temperature (Jones, 1999). Although the strain-stress curve can be studied by using the conventional mechanical testing instruments, the DMA is more applicable. The reason is, during analysing a material using a traditional

technique the test is achieved at a constant temperature and/or constant rate per sample.

The DMA technique provides us with both the elastic (E') and the viscous component (E''). The elastic ad viscous components (E' and E'') both are very useful to obtain different rheological parameters such as creep response, tan delta, and complex viscosity. In addition, these parameters are very significant for the modelling of viscoelastic materials. Polymers are viscoelastic fluids, which have viscous and elastic behaviour, and they behave according to how fast they flow or are deformed. For example, glass transition temperature and damping behaviour can be used to determine material's using conditions such as temperature, stiffness (Jones, 1999) (Isreb, 2011). In addition, DMA measurements explain how a material behaves at the moment and future.

For its high sensitivity DMA becomes very applicable technique for the following tests: to evaluate the mechanical properties of a material, to study the morphology of polymers, loss factor (Tan delta), loss angle (delta), impact resistance, dynamic viscosity, curing kinetic, correlation with materials formulation, ageing, damping, glass transition temperature (Tg), industrial products stiffness, rheological properties, secondary transitions, specimen stiffness, young Modulus, thermal stability, creep behaviour, tension test, stress-strain, vs. Dynamic Mechanical Analysis of Epoxy-Carbon Fiber Composites (Perfetti et al 2010) (Isreb, 2011)

The DMA was used in two modes. The first was to measure the Tg of the samples. Rectangular samples (Length, Width, and Thickness) with dimensions 8 mm, and about 12.6mm, 0.34mm (L, W, and T) respectively

were analysed by DMA using dual cantilever clamp and the DMA was set on Multi-frequency-strain mode. . Temperature from 25°C to 150°C at a ramp rate 3 C°/min at different frequency rates (0.1 Hz, 1 Hz, 10 Hz, and 100 Hz) were applied. Universal analysis 2000 version 4.3A was used to analyze the resultant graphs.

The second test was carried out to determine the rheological properties of the sample. In this test the tensile clamp was used to analyse the samples in isolation mode. Frequency sweep tests were conducted. The temperature was adjusted to 0°C, held for 3 min isothermally, and then a frequency sweep was applied at a constant strain value of 0.1% using frequency rate range of 0.1-100 Hz. Afterword the temperature was elevated by 10°C and the test was repeated again. This was repeated until the sample is damaged (Cespi et al, 2011) (Isreb, 2011)

2.3.7 Shear Rheometry

The term rheometer refers to the technique used to measure the flow behaviour of viscous and viscoelastic materials in response to applied force. In some cases rheometer is more applicable to be used for some fluids which cannot be evaluated by a single value of viscosity and therefore require more parameters to be set and measured than is the case of a viscometer. Based on the applied stress, there are two different types of rheometers: shear sheometer in which the applied shear stress or shear strain can be controlled, and extensional rheometer in which an extensional stress or extensional strain is applied. In this research work plate shear rheometry was used to evaluate the rheological properties of the coating film of ethylcellulose. It is composed of two plates, stationary plate on the bottom

side and rotating plate at the upper side. The rotating plate is available in two different shapes, flat and cone-shaped. The upper plate rotates generating a shearing stress on the sample on the stationary plate. This instrument based on applying a shear stress on a sample and measures the strain within the sample. It is able to measure different mechanical and rheological properties such as loss modulus, storage modulus and complex viscosity (Isreb, 2011) (Mezger, 2006)

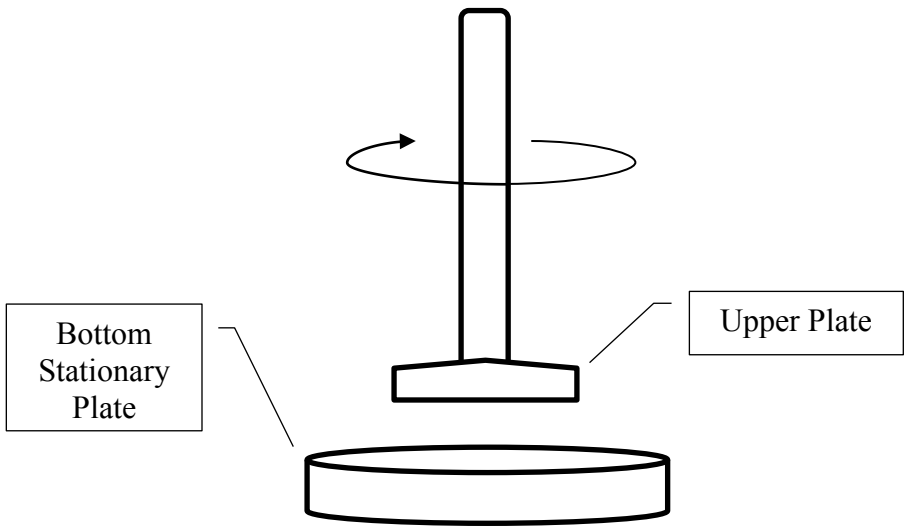

Figure 2-2: The Cone and Plate Shear Rheometer. (adapted with modification from http://www.ipc.uni-stuttgart.de)

In this study sample of free casting film of ethylcellulose was tested using Parallel Plate Shear Rheometer (PPSR). The zero gap was set between the plate base and the upper plate. Each sample was flattened on the stationary plate and the temperature was controlled. The distance between the two plates was adjusted to 0.25 mm, and then the system was left until the

normal force was less than 1N. During the experimental work three different tests were carried out to the film samples in the following order:

2.3.7.1 Determination of the linear viscoelastic range (LVE)

The linear viscoelastic region of the samples can be determined by strain amplitude sweep test, in order to select the proper strain value to apply in the frequency sweep test. The angular frequency and strain range were adjusted 1 s^{-1} and 0.1-10% respectively. The tests were carried out into two different sets based on the film formula. Plasticised films were heated from 70 to 150 °C, while non-plasticised films were heated from 70 to 200 °C (Cespi et al, 2011)

2.3.7.2Frequency sweep test

During this test the samples were subjected to an oscillatory shear at strain amplitude of 3%, as it was obtained from the LVE test as explained above (within the LVE range). Both storage and loss moduli were measured over an angular frequency range of 0.01-100 s^{-1} allowing the calculation of the complex viscosity values to be able to compare the obtained results from the DMA to the shear rheometer, the linear frequency obtained by the DMA was converted to angular frequency. Also, complex viscosity was calculated using the rheoplus software version 3.4)

2.3.8 The process of pellets coating

In this research work Caleva Mini coater was used. It was selected as a coating machine in this research work because it can coat a small batch (making it ideal for the purpose of this work) and because it is an open

system which means that organic solvents can be used in coating (under fume cabinet). Other closed systems cannot handle organic solvents for fear of flammability. . Samples weighing 30 gm of theophylline pellets, with a diameter from 0.8 to 1.2 mm, was coated using Caleva Mini Coater®. The coating solution was prepared by dissolving 10% w/v ethylcellulose in ethanol and 10% w/w (of the polymer weight) TEC as plasticizer. samples were coated to different coating levels (2.5, 5, and 7.5% w/w). The air flow was adjusted to 50%, agitator was at 30%, the temperature was adjusted to 28^{o}C and the spray rate was 3 ml/min.

2.3.9 Compression of uncoated and coated pellets

Samples of 200 g of uncoated and coated pellets were directly compressed using a compaction simulator. Three variables were studied which are: coating level (% w/w), compression force applied during pellets' tabletting, and compression time (dwell time). Multifactorial design was applied by using Minitab software (version 16) for statistical analysis, to study the factors that might affect on the kinetic profile of the final products. In this research work, the pellets were compressed directly without adding additives like cushioning agents, to study the durability of the coating film.

2.3.10 Dissolution of Theophylline pellets

In vitro dissolution test is carried out to validate initial screening among potential formulations to identify the effect of significant manufacturing factors and to facilitate in the selection of candidate formulation. The dissolution test can accelerate the formulation development, enabling a prompt identification of potential problems in drug release (Missaghi et al

2005) (Joshi et al 2008). In vitro dissolution studies of theophylline pellets were inspected based on the dissolution test (USP XXVII rotating paddle method). The dissolution test was achieved at 37 ±0.5 °C using 900 ml of distilled water for 6 hours. one gram of uncoated pellets and coated pellets of 2.5, 5 and 7.5% coating film load was added to each vessel and the release of theophylline was measured by taking 5 ml sample each 30 min for the first two hours then one sample each hour. In order to keep the volume of the medium constant, fresh 5 ml of distil water was added each time to replace the withdrawn samples (dissolution medium was 900ml in volume). UV spectrophotometery was used to analyse the samples at a wavelength of 272 nm (Kucera et al, 2008) (Melegari et al, 2016)

Chapter 3

Thermal analysis and characterisation of the film coating formulation

3. Chapter 3: Thermal analysis and characterisation of the coating formula

3.1 Introduction

Thermal analysis is a significant technique to evaluate the level of film coating formation, and to estimate an appropriate curing temperature. It is a useful method to study polymer and polymer containing samples. Recent polymeric materials are generally mixtures with complex morphologies that are important to evaluating their material properties. Thermal analysis tools are helpful for find more morphological information for these kind of systems

This Chapter focuses on the thermal behaviour of the cast films using different levels of additives and evaluates the changes on the thermal transitions of the coating film.

3.2 Results and discussion

In this chapter the physical appearance, microscopic observation and the thermal characterisation of the free film were studied

3.2.1 External and microscopic study of the cast films

Different samples of free films with different levels of TEC and PEG400 were prepared and examined. The percentage of TEC and PEG400 were calculated as a weight-by-weight percentage of the dry ethylcellulose (Coating polymer). The films were observed visually as shown in Tables 3-1 and 3-2.

Free film samples, formulated without adding any plasticizer, were clear in

appearance and were not easily peeled off from the acetate sheet without breaking. Furthermore, the films were very fragile and the edge of the film was irregular and rough, which might be because of the elevated internal stress. (Rowe, 1981) (Rowe, 2007)

When TEC was used as plasticizer, the higher the level of the plasticizer the more flexible the film. The films were almost clear as in the case of 0% plasticizer. In addition, by increasing the level of TEC, it was obvious that the edges were smoother and the films were easy to remove from the acetate sheet without breaking, indicating less internal stress (Table 3-1) (Sakellariou et al, 1986) (Isreb, 2011).

In case of using PEG400 as plasticizer, the prepared films became cloudier as the level of PEG400 increased, and white spots slightly appeared when 10% of PEG400 was used. Using 20% PEG400, the films were full of white spots and at 30% PEG400 the film was all white. The edges were smooth which indicates the films have less internal stress in comparison to non plasticised films (Table 3-2). This shows that PEG400 is plasticising the polymer to a point, after which a phase separation was occuring. This can be compared to when TEC was used, when the films were clearer and more flexible. (Rowe, 2007)

Table 3-1: Some visual notes were taken for free films with different levels of TEC

Sample No.	% TEC	Physical appearance	Comments
1	0%	Clear films were obtained	Tilted edges and brittle
2	5%	Clear	Tilted edges and brittle
3	10%	Clear	Easily removed from the acetate sheet
4	20%	Clear	Flexible and easily removed
5	30%	Clear	Soft edges, flexible and easy removed from acetate sheet

Table 3-2: Some visual notes were taken for free films with different levels of PEG400

Sample No.	% PEG400	Physical appearance	Comments
1	0%	Clear	Brittle, and irregular edges due to high internal stress
2	5%	Cloudy	Brittle with tilted edges
3	10%	Cloudy film with small number of white spots	Smooth edges and easy removed from acetate sheet
4	20%	Very cloudy and large number of white spots	Flexible and easy to removed from acetate
5	30%	The prepared films were all white and Opaque	Flexible and easy to removed from acetate

The free films were examined using Scanning Electron microscope (SEM), and the effect of plasticiser level was studied. A number of images for each formulation were taken to observe the homogenecity of the films contents. The images presented in Figures 3-1, 3-2 and 3-3 show the ethylcellulose film without plasticizers and with plasticizer at several levels. Furthermore, by increasing the level of PEG400, the free films revealed white spots, and these spots started to increase till it covered all the surface of the free film

(as shown in the appendix). Phase separation between EC and PEG400 has been documented before even at 25% w/w level (Vesey et al, 2005)

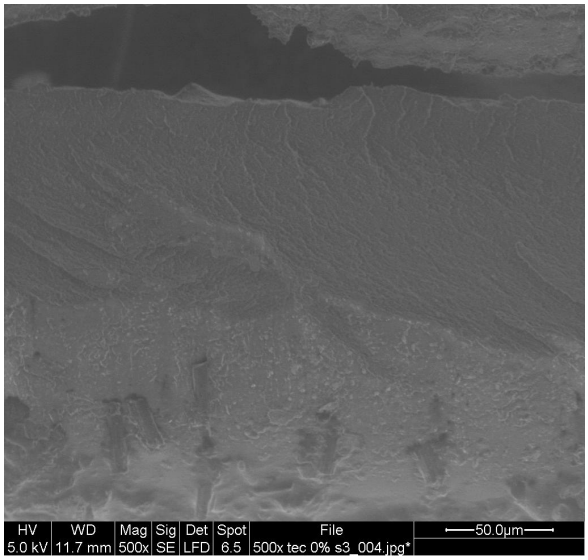

Figure 3-1: SEM image of non plasticised ethylcellulose film

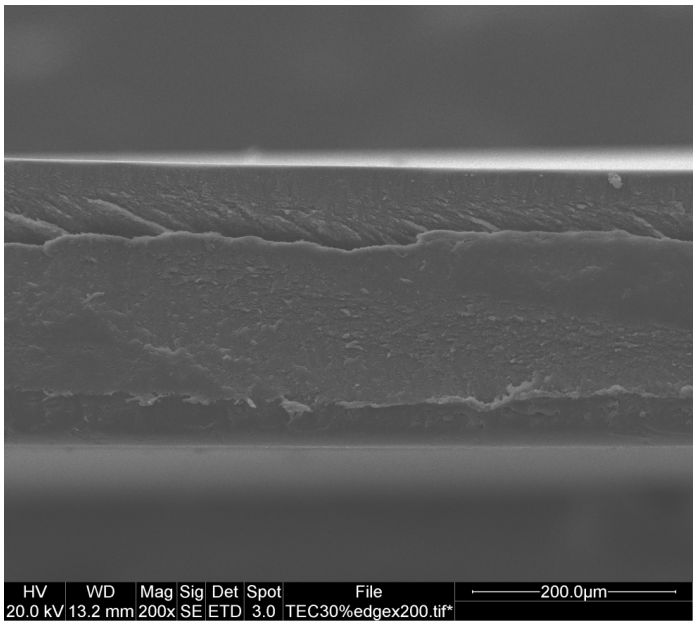

Figure 3-2: SEM image of edge of ethylcellulose film with 30% TEC

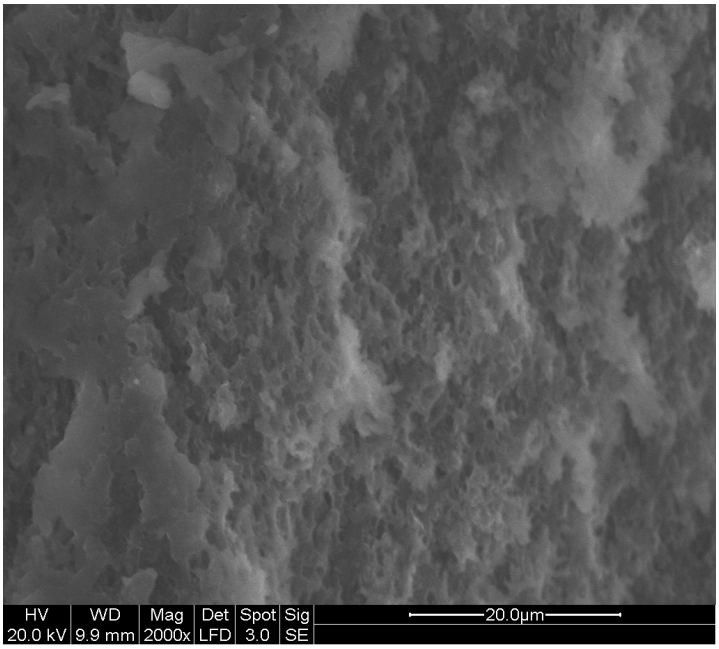

Figure 3-3: SEM image of ethylcellulose with 30% PEG400

3.2.2 Thermal gravimetric analysis study of the cast films

TGA technique was used to analyse the free films of ethylcellulose with different level of plasticiser as demonstrated in section 2.2.3. TGA was used to measure moisture content by measuring the weight loss below 100 C°, the onset and the end point of the transition are demonstrated in table 3-3.

The results shown in Figures 3-4 to 3-6 illustrate the thermal behaviour of free films using different formulations. The curves show that the degradation is completed in two distinctive steps without a plasticiser, while it appears to happen in one step when plasticiser was added. In case of using different levels of TEC, it was obvious that the decomposition onset temperature decreased by increasing the level of TEC. This was expected in accordance to the literature (Isreb, 2011). It can be concluded that TEC evaporating/decomposing is starting first and continue to overlap that of the

polymer. On the other hand, when different levels of PEG400 were used, there was no change in the decomposition onset temperature. This could be explained due to the evaporation/decomposition of PEG 400 starting after that of the polymer.

The moisture content of the films plasticised with PEG 400 was greater than those for the films plasticised with TEC (Tables 3-3 and 3-4). This can be attributed to the hydrophilicity of PEG 400. Despite both plasticizers being hydrophilic, PEG 400 is the most hydrophilic (Thomas et al 1990).

Table 3-3: TGA results of free films without and with different levels of TEC

Plasticizer level TEC	**Moisture content (%)**	**Onset temp. (°C)**	**End temp. (°C)**
0%	0.9 ± 0.1	211.8 ± 0.6	275.1 ± 0.3
5%	1.5 ± 0.2	153.8 ± 0.5	250.9 ± 1.1
10%	0.6 ± 0.1	144.9 ± 0.7	234.5 ± 0.5
20%	0.6 ± 0.1	141.8 ± 0.3	227.3 ± 0.2
30%	0.6 ± 0.1	119.2 ± 0.5	188.8 ± 0.6

Table 3-4: TGA results of free films without and with different levels of PEG400

Plasticizer level PEG400	Moisture content (%)	Onset temp. (°C)	End temp. (°C)
0%	0.9 ± 0.1	211.8 ± 0.6	275.1 ± 0.3
5%	1.3 ± 0.1	207.1 ± 0.8	248.2 ± 0.3
10%	1.1 ± 0.5	206.2 ± 0.7	248.4 ± 0.5
20%	1.5 ± 0.1	207.8 ± 0.4	254.9 ± 0.7
30%	1.8 ± 0.1	204.3 ± 1.1	246.4 ± 0.5

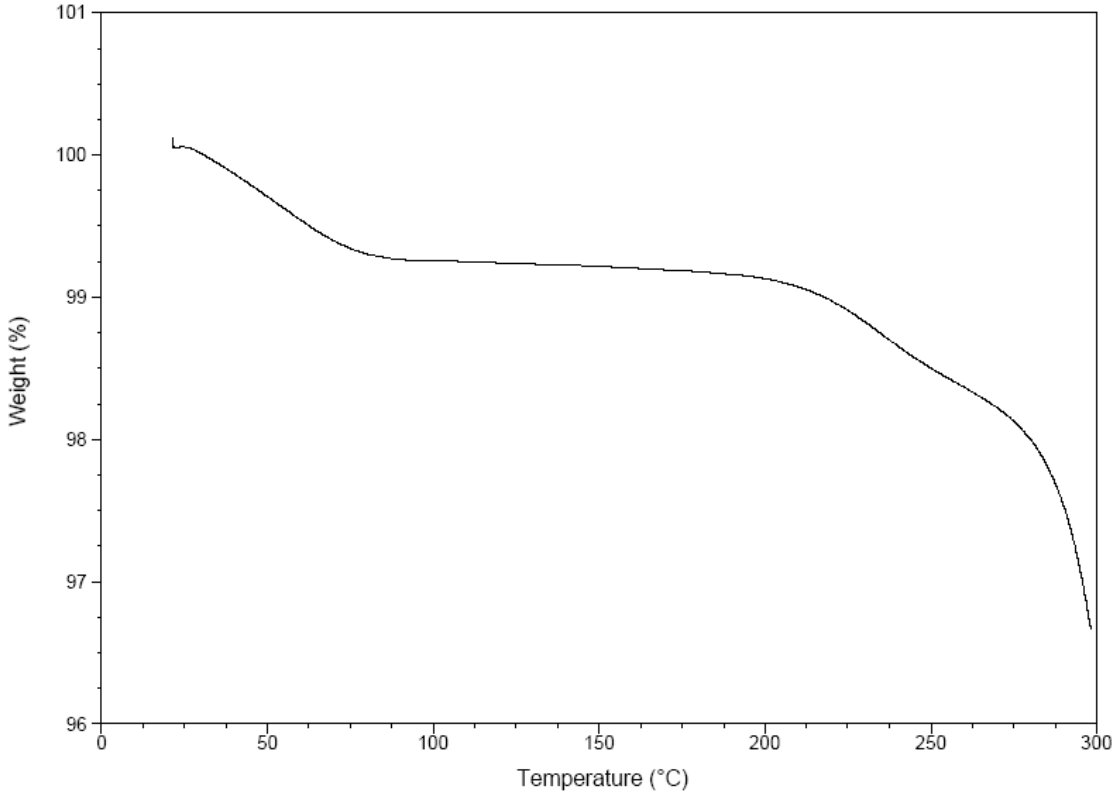

Figure 3-4: TGA study of a free film of ethylcellulose without additives

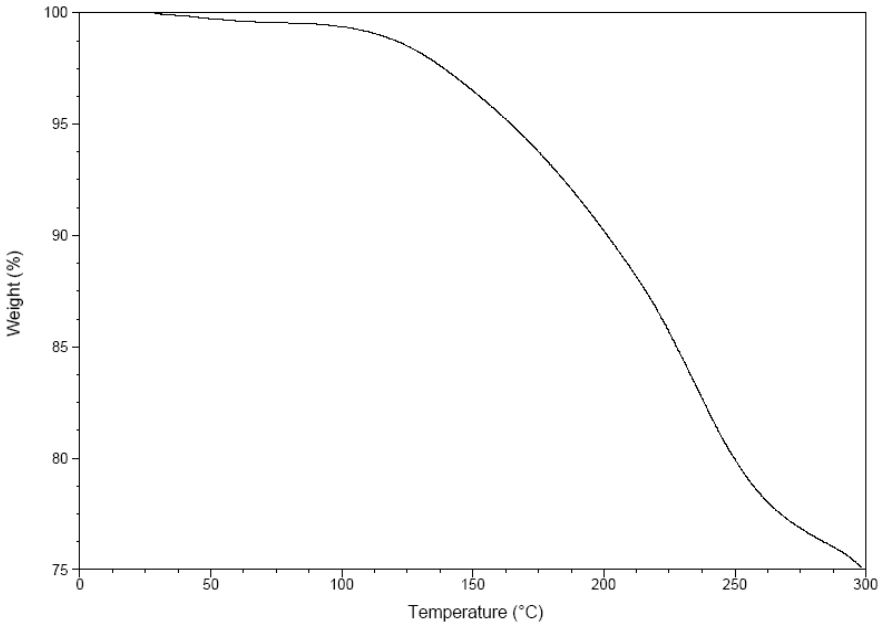

Figure 3-5: TGA study of free film of ethylcellulose with 30% TEC

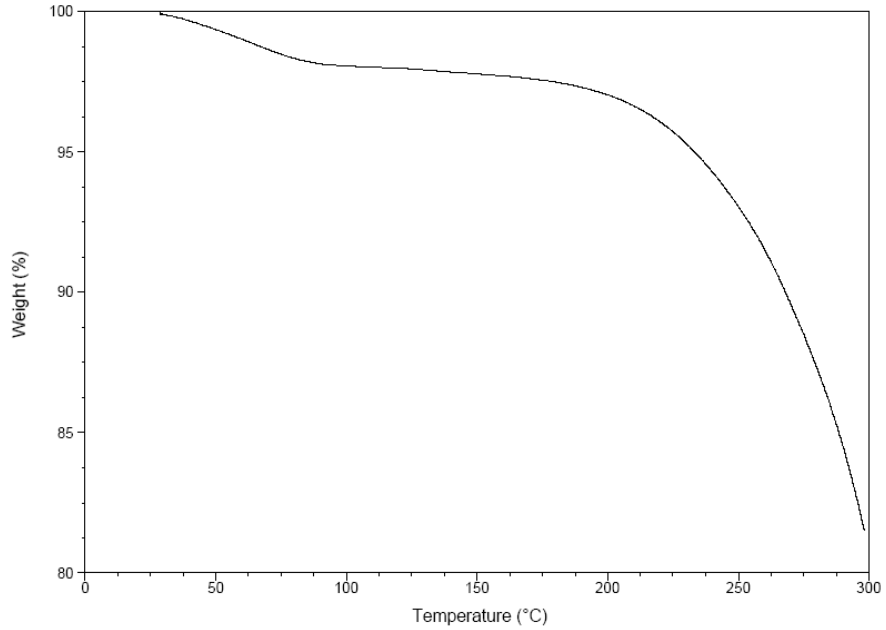

Figure 3-6: TGA study of free film of ethylcellulose with 30% PEG400

3.2.3 Differential Scanning Calorimetry analysis of the cast films

The thermal behaviour of ethyl cellulose films with and without plasticizer was studied using Differential Scanning Calorimetry as demonstrated in section 2.2.7. The thickness of samples was adjusted in both DSC and DMA methods to ensure the consistency of the results. In order to achieve that, a thermal hydraulic press was used to adjust the thickness to 0.35 mm. Initially the samples were analysed using the DSC with a temperature ramping method, in which the samples were heated from room temperature to a point above their glass transition temperature. The Tg value was not clear as it was overlapping with the moisture content in the sample, as seen in Figures 3-7 and 3-8. Therefore the heat-cool-heat mode with a pin-holed pan lid was used to evaporate the moisture from the film. Figure 3-9 illustrates the interference between the moisture evaporation endothermic and the Tg step during the first cycle, but by increasing the temperature above 100 C° the evaporation occurred and during the second cycle the sample was free of moisture and the Tg value was much clearer. Furthermore, increasing the heat above the Tg of the film allows the plasticizer to disperse between the polymer chains. During the first and second heating cycle there was a peak which may represent the melting of ethyl cellulose and it was seen on the cooling cycle as a peak of recrystallisation. By increasing the level of TEC both melting and recrystallisation peaks disappeared which can be explained as TEC changed the nature of the coating polymer to be more amorphous in nature (as shown in Figure 3-10) (Hyppölä et al, 1996).

In films plasticised with PEG 400 (Figure 3-11), the evaporation of the moisture content in the film was seen as a wide endothermic peak between 40-100°C the Tg of the polymer appears at 127 °C which is in agreement with the value reported in the literature (Hyppölä et al., 1996). At higher temperature, another peak was seen which represents the melting of the coating polymer from 170 to 210 °C, and during the cooling cycle a recrystallisation peak was seen. The presence of the melting and recrystallisation peaks mean ethylcellulose films plasticised with PEG 400 remained semi crystalline.

Table 3-5 summarises the Tg values of films plasticised with different concentrations of TEC and PEG 400. It can be seen that the Tg value decreases as the concentration of TEC in the film increases whereas the increase of PEG 400 concentration above 10% does not appear to have an effect on the Tg value of the film. It can be therefore concluded that PEG 400 is phase separating above 10%(Table 3-5, Figures 3-13 and 3-15). It has to be noted that the Tg value of films plasticised with PEG 400 was measured to be higher than the 70 °C reported in the literature (Vesey et al, 2005). However this could be because they have reported the Tg from the first run in which the film was heavily plasticised with water as well. Moreover it is not clear if they have used the onset to determine the Tg value. In all cases the fact that they reported that films plasticised with TEC and PEG to have similar Tg values indicates that they were using the first heating cycle (in which there is more moisture content in the PEG films accounting for the further suppression of the Tg value).

Tablet 3-5: Plasticiser concentration vs. Tg values

Plasticiser %	Tg with TEC (°C)	Tg with PEG 400 (°C)
0%	127 ±3	127 ±3
10%	88.9 ± 1	102 ±2
20%	55.8 ± 2	105 ±0.5
30%	38.8 ± 1	108 ±0.5

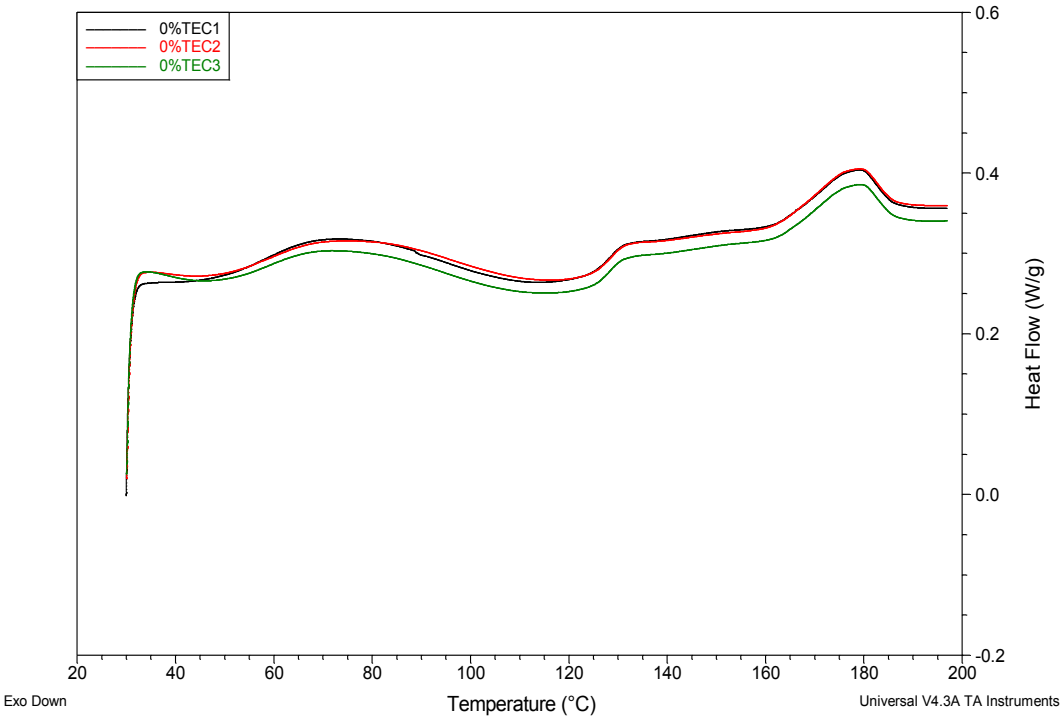

Figure 3-7: Triplicate DSC graphs of unplasticised ethylcellulose films in the first heating cycle of the DSC scan

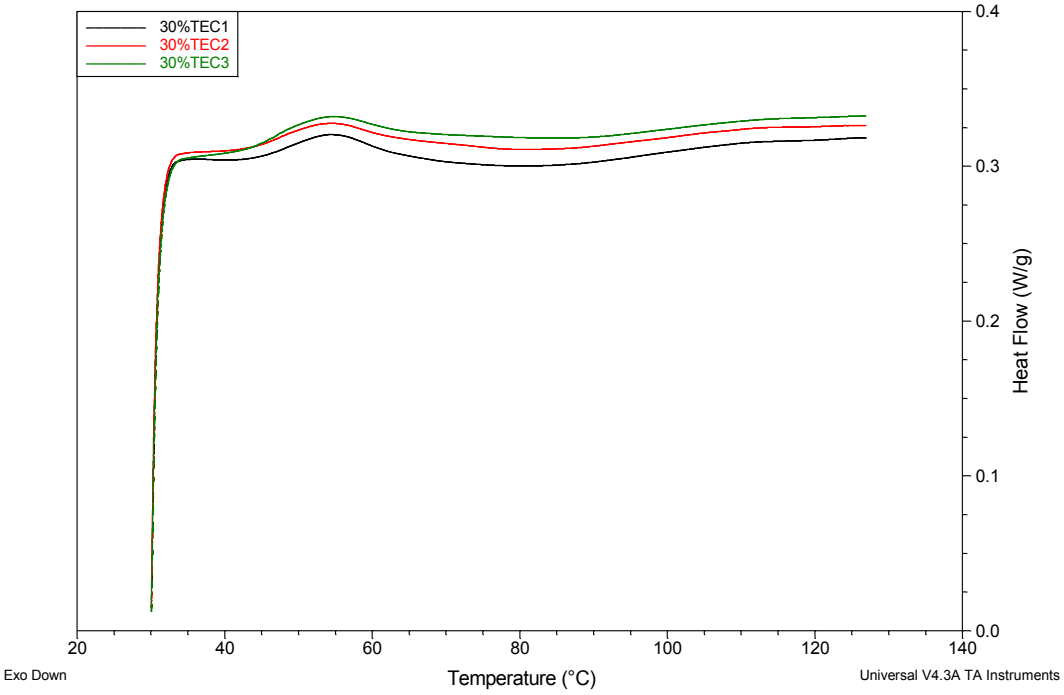

Figure 3-8: Triplicate DSC curves of ethylcellulose film with 30% TEC in the first heating cycle of the DSC scan

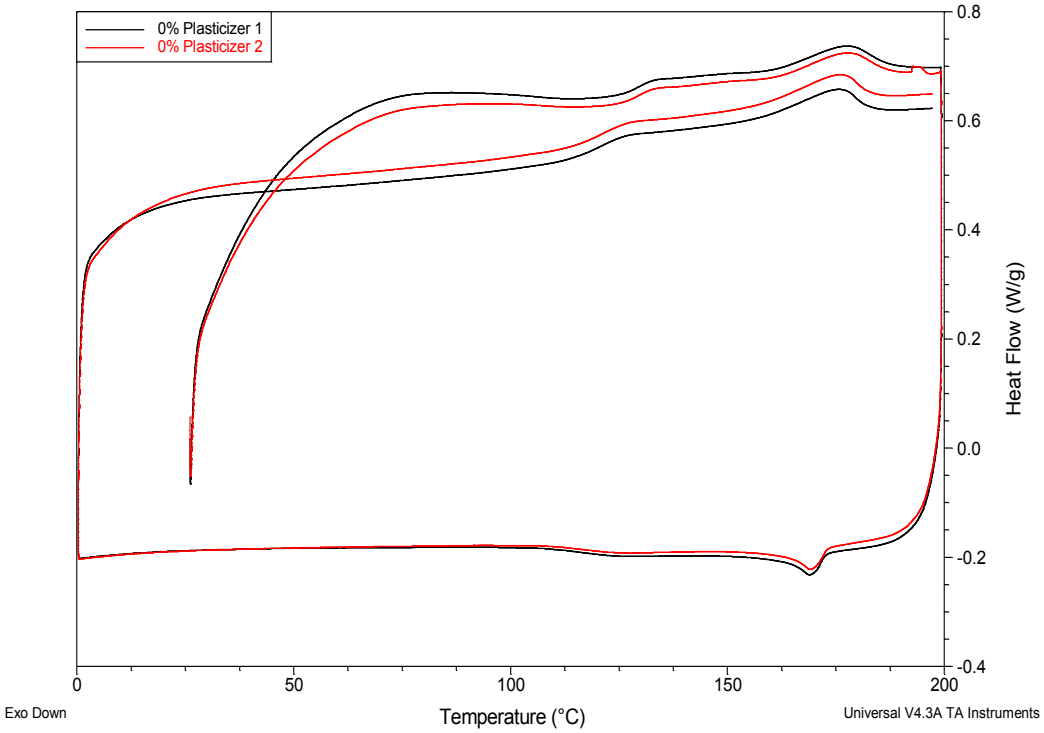

Figure 3-9: Heat-cool-heat DSC thermogram of two unplasticised ethylcellulose free film samples

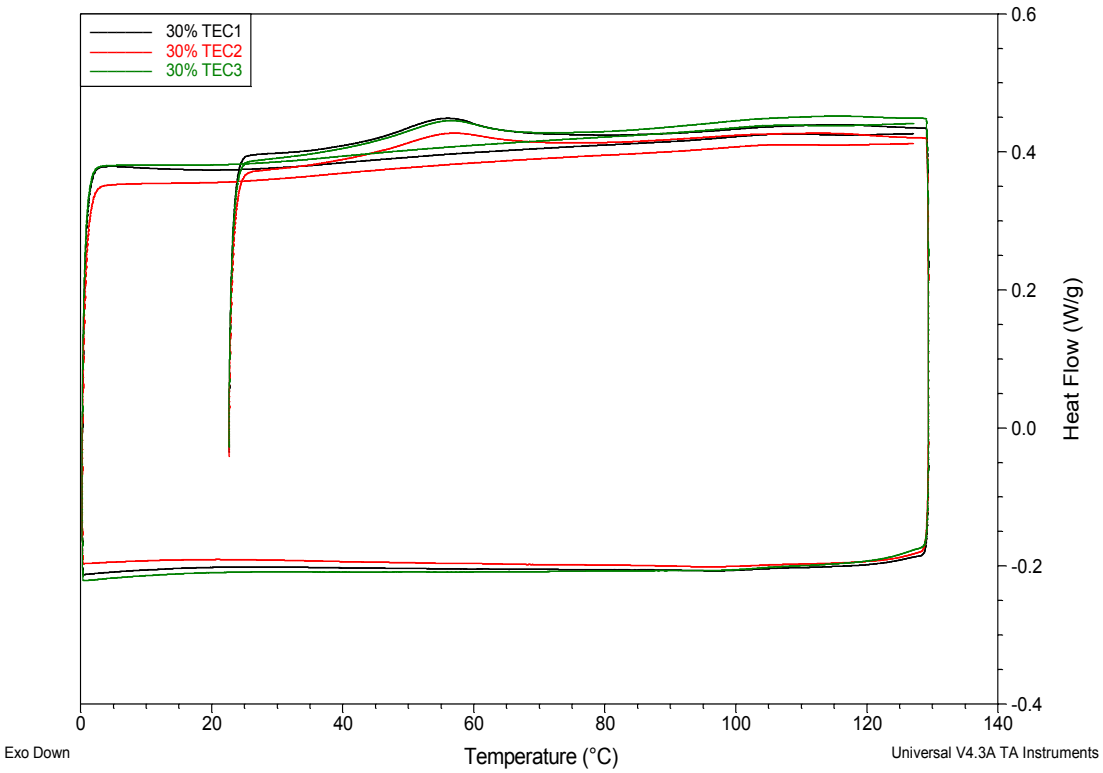

Figure 3-10: Heat-cool-heat DSC thermogram of free film of ethylcellulose plasticised with 30% TEC

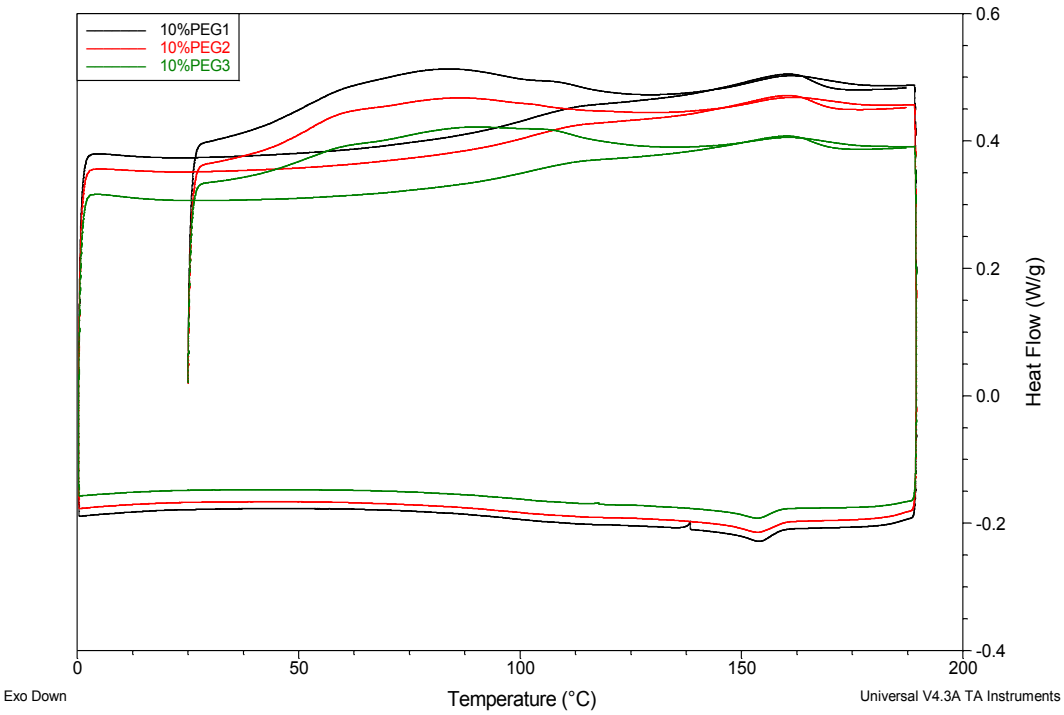

Figure 3-11: Heat-cool-heat DSC thermogram of ethylcellulose free film plasticised with 10% PEG400

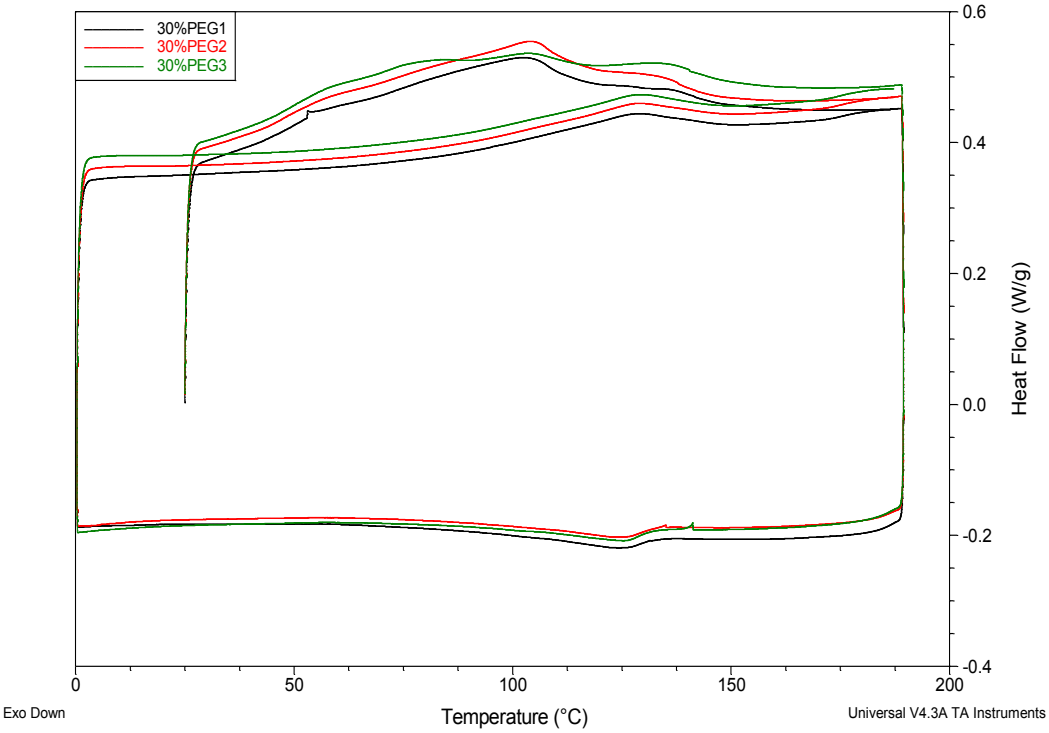

Figure 3-12: DSC study of ethylcellulose free film with 30% PEG400

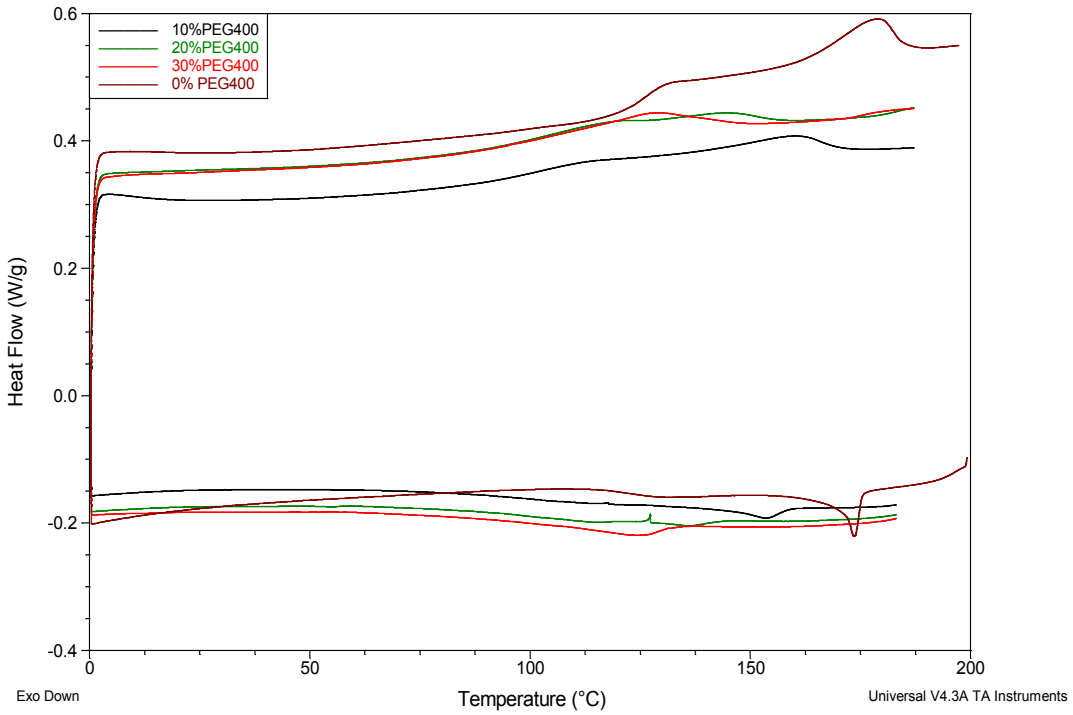

Figure 3-13: DSC thermogram of the cool and the second heating cycle of ethylcellulose film plasticised with 0, 10, 20 and 30% of PEG400

3.2.4 Dynamic Mechanical Analysis of free film

Dynamic Mechanical Analysis technique was used to analyse the thermal mechanical properties of ethylcellulose films without or with various levels of plasticizers. When the DMA was used to measure the Tg values for the different samples, only first run cycle was achievable as the samples deform when the cycle goes above the Tg value. For this reason only first run cycle was applied when DMA was used to analyse the samples. On the other hand during the DSC analysis studies, two heating cycles were applied to the sample to measure the Tg without moisture interference. The samples were analysed as explained in section 2.2.8.

3.2.4.1 Effect of Frequency or strain rate on the glass transition temperature

The effect of frequency value on the measured storage modulus, loss modulus and tan delta was investigated. The samples were analysed by DMA using constant frequency with continuous heating in multi-frequency strain mode. Figure 3-14 to 3-17, show the study of storage and loss moduli vs. temperature of ethyl cellulose free film with 3 frequency rates 1, 10 and 100 Hz.

The plots of loss modulus E'' is characterised by an asymmetrical peak with a smaller slope at the low temperature part than at the high temperature part upon heating, which is an indication for the distribution of intrinsic structural relaxation times. It was obvious during the study of loss modulus vs. temperature that the onset and inflection point temperatures were shifted to higher value by increasing the frequency. This is expected since at higher frequency, more free movement of the atoms will be needed to match the imposed frequency and this can be attained at higher temperature (Turi, 1997).

In Figure 3-19, the plot of tan delta vs. temperature for free films of ethyl cellulose was constructed. The Figure shows the mechanical behaviour of free films of ethyl cellulosed without additives when different frequency rates of 1, 10 and 100 Hz were used.

The measured Tg value was at: 131 °C at 1 Hz, 134 °C at 10 Hz and 142 °C at 100 Hz and since the Tg of ethylcellulose as mentioned in the literature is 130 °C ±2 (Lai et al, 2010) (Albertini et al, 2016), this indicated that 1 Hz was

the most appropriate frequency to be used in this experimental work for direct comparison with DSC data.

3.2.4.2Clamp size

Free film of ethyl cellulose with 30% PEG400 was analysed using two different size of dual cantilever clamps small (8 mm) and large (35 mm). The results show a significant difference between the small and large clamp. It was visually obvious the film analysed using large clamp was saggy and ruptured as it lost its elasticity under the Tg of the film. Using the small clamp, the film was intact up until the Tg value and revealed proper Tg. Based on this result the small clamp was used during the DMA studies as shown in figure 3-20. It is interesting to note that the literature offers little in terms of comparing the effect of clamp size.

3.2.4.3Evaluation of the Tg for free films using DMA

The film was directly affected by the level of plasticiser as shown in Table 3-5. By increasing the level of plasticiser the Tg value decreased. In case of using TEC as plasticiser, the decline of the Tg value was obvious and continued from 0%, 10%, 20% and 30%. That means the distribution of the plasticiser into the coating polymer increased leading to more plasticised film (Qussi et al, 2006)

Tablet 3-6 also illustrates the influence of adding PEG400 to the coating film, where the value of Tg decreased by increasing the level of PEG400, and that was clearly seen in 0%, 10% and 20% PEG400. However, there was no significant difference in the values of Tg between 20% and 30% PEG400, which can be contributed to the level of saturation of the film that was seen

as a white spots visually and cloudy images of the film when SEM was used. This is similar to the effect noticed in the DSC and serves to confirm our finding and the importance of using the second heating cycle in the DSC rather than the first. It also shows that DMA can be used to determine the effect of plasticisers in isolation of the moisture content of the sample. This could be an advantage or a disadvantage depending on the goal of the experiment. In all cases it is something worth keeping in mind when performing Tg determination via DMA.

Tablet 3-6: Plasticizer concentration vs. Tg values

Plasticizer %	Tg of TEC (^{o}C)	Tg of PEG 400 (^{o}C)
0%	131 ±1	131 ±1
10%	98 ± 3	113 ±0.5
20%	78 ± 2	108 ±1
30%	67 ± 2	109 ± 1

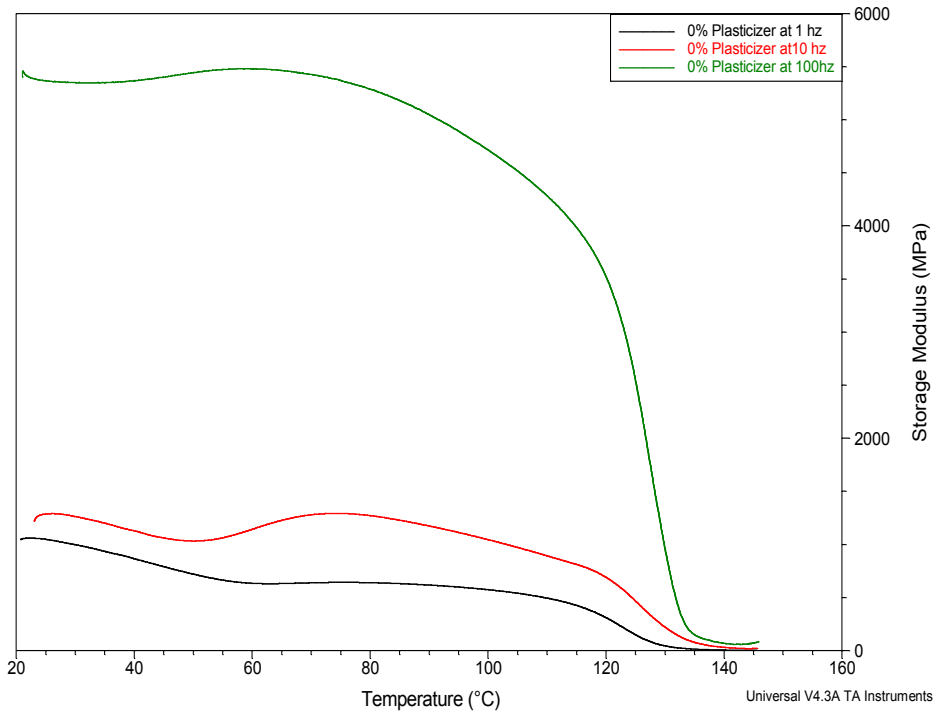

Figure 3-14: Plot of storage modulus with temperature at frequencies 1, 10 and 100 Hz

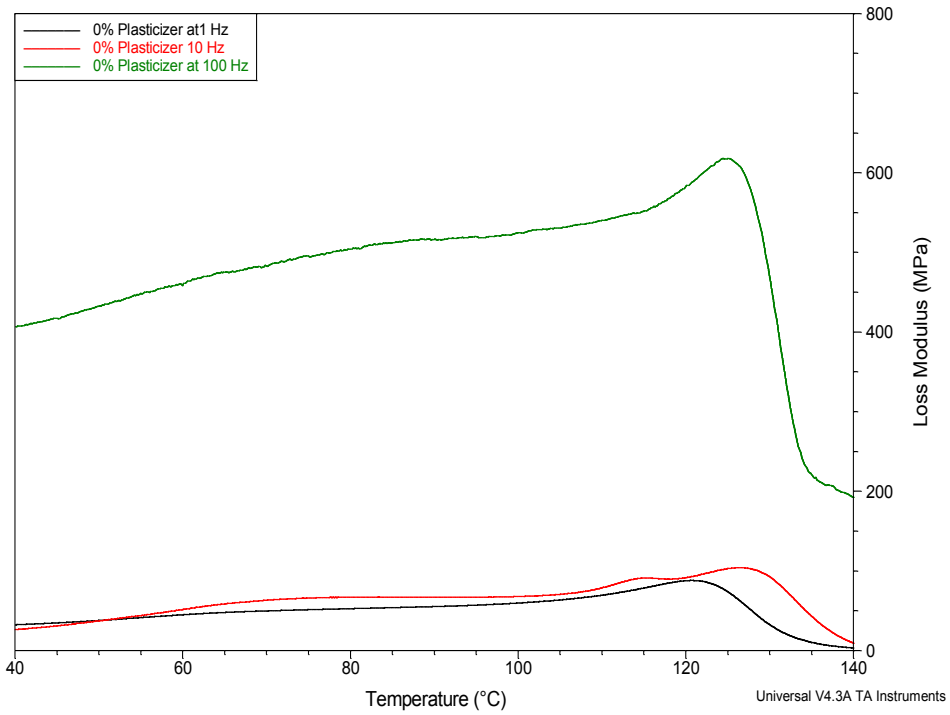

Figure 3-15: Plot of elastic modulus with temperature at frequencies 1, 10 and 100 Hz

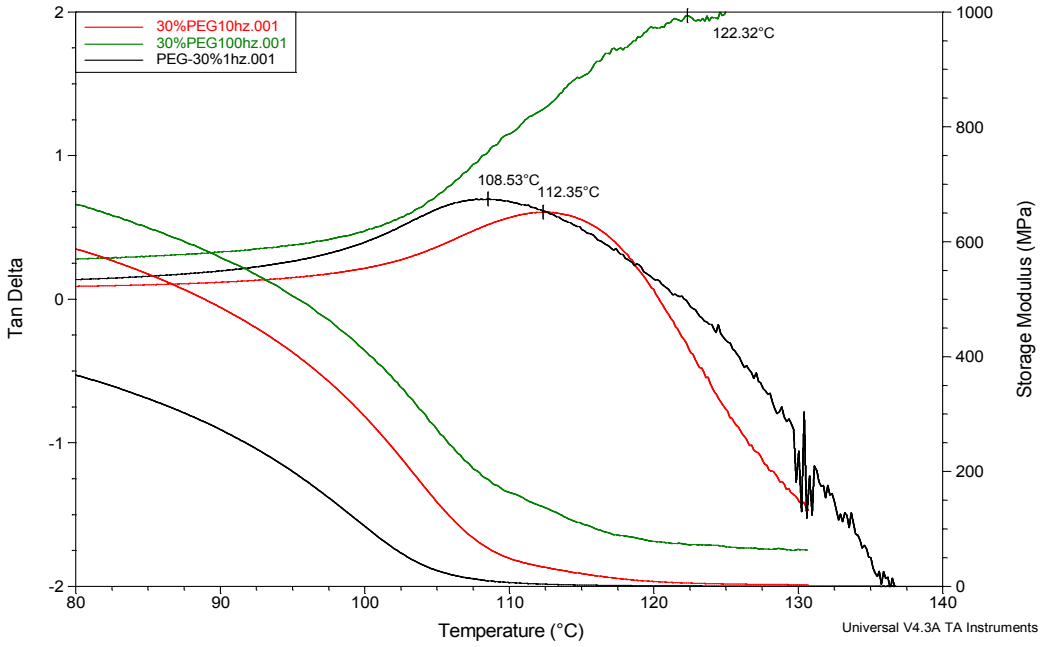

Figure 3-16: Plot of both storage modulus and tan delta vs. Temperature at frequencies 1, 10 and 100 Hz for films with 30% PEG400

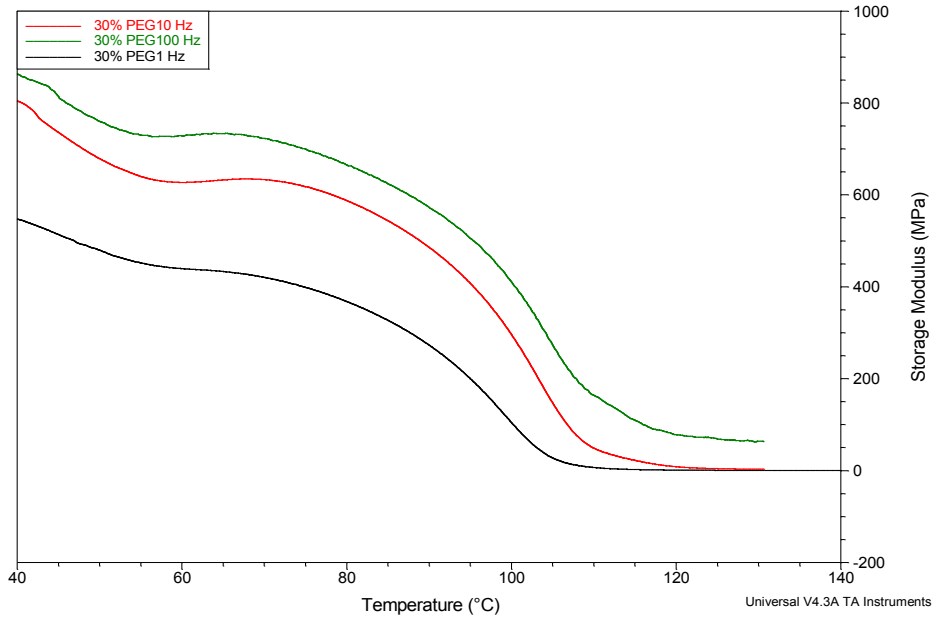

Figure 3-17: Plot of storage modulus with temperature at frequencies 1, 10 and 100 Hz for films with 30% PEG400

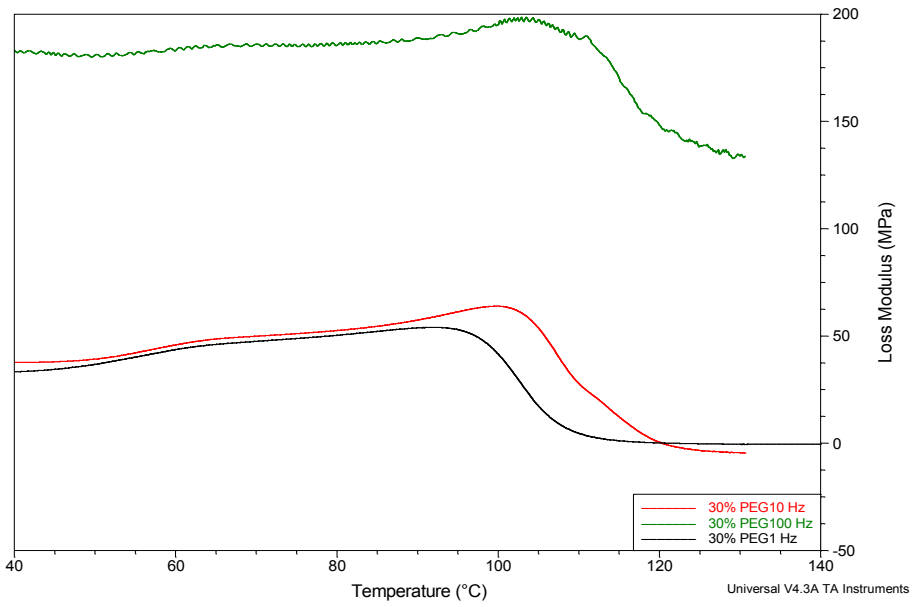

Figure 3-18: Plot of loss modulus with temperature at frequencies 1, 10 and 100 Hz for films with 30% PEG400

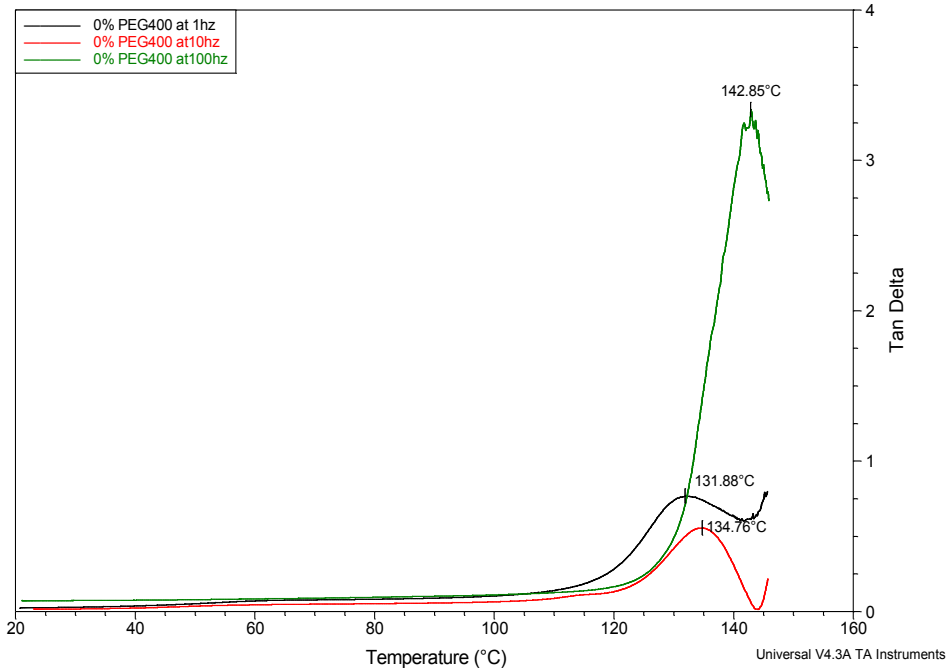

Figure 3-19: Plot of tan delta with temperature at frequencies 1, 10 and 100 Hz for films without additives

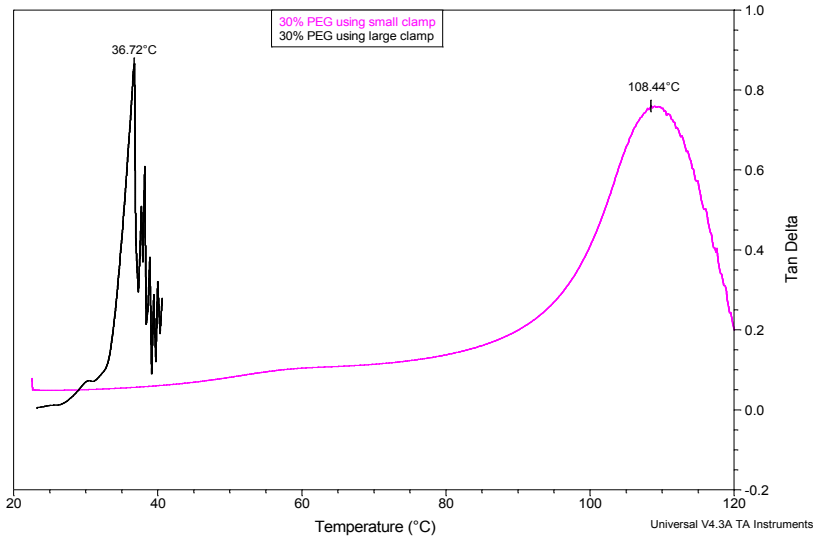

Figure 3-20: Plot of tan delta with temperature at 1 Hz for films with 30% PEG400 using large and small size of dual cantilever clamps

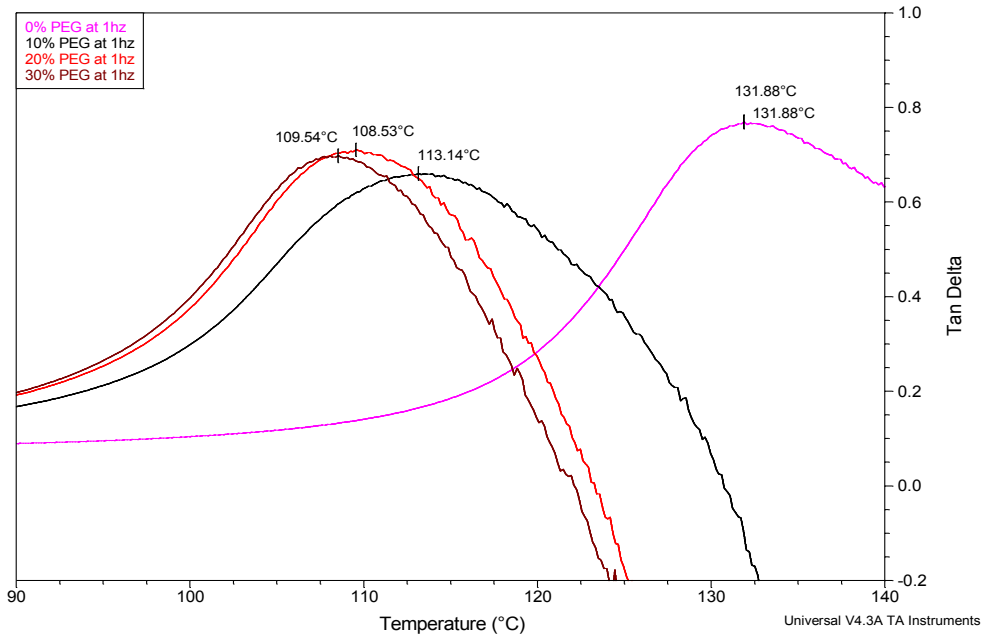

Figure 3-21: Glass transition temperatures of ethylcellulose films with different levels of PEG400 measured from tan delta of the DMA

3.2.5 Conclusion

From the TGA results of ethylcellulose films using TEC as plasticiser, it can be seen that the degradation onset increased by increasing the level of TEC. In contrast there was no change in the degradation onset temperature when different levels PEG400 were used. This is attributed to the higher degradation temperature of PEG 400. Moreover PEG containing films have relatively higher moisture content that those with TEC.. Both DSC and DMA identified that TEC is more efficient plasticiser for EC films than PEG 400.. When 10% of PEG400 was used, there was slightly reduction in the Tg of the coating film, however, at 20 and 30% there was no noticable changes in the Tg. That was attributed to the phase separation of the excess plasticiser which was evident in the visual observation of the cast film . On the other hand, using TEC and at different levels there was remarkable lowering in the Tg. (Bodmeier et al, 1994)

The Tg values obtained by DMA were always higher than the Tg values obtained by DSC, since the glass transition is a kinetics driven phenomenon, and the sample size used in DSC was smaller than in DMA, that's why there were difference between the obtained results from the two techniques (Queiroz et al, 2010). It can be concluded that TEC is a better overall plasticiser than PEG 400.. That is in agreement with the literature (Bechard et al, 1994) (Fadda et al, 2010)

Table 3-7: The results of Tg values obtained by DSC and DMA

Plasticizer %	TEC Tg value (°C) by DSC	PEG400 Tg value (°C) by DSC	TEC Tg value (°C) by DMA	PEG400 Tg value (°C) by DMA
0	127 ±3	127 ±3	131 ±1	131 ±1
10	88.9 ±1	102 ±2	98 ±3	113 ±0.5
20	55.8 ±2	105 ±0.5	78 ±2	108 ±1
30	38.8 ±1	108 ±0.5	67 ±2	109 ±1

Chapter 4

Study of the chain dynamics, rheological and mechanical properties of film coating

Chapter 4: Study of the chain dynamics, rheological and mechanical properties of film coating

4.1 Introduction

The coating process was discussed previously on 1.12.1. In this chapter, the rheological properties of ethyl cellulose coating film were studied using dynamic mechanical analysis (DMA) and shear rheology and the effect of plasticisers on these properties. Different level of plasticizers (TEC and PEG), 0, 10, 20 and 30% were used.

4.2 Aims and objectives

This chapter aims at gaining an insight into the rheological characteristics of various plasticized ethyl cellulose films in order to predict the behaviour of the coat under coating as well as compression conditions. If the film has a dominant elastic behaviour under compression conditions the film might crack leading to an increase in drug release or even dose dumping. The results will be compared to the dissolution data of the compressed pellets in the next chapter.

It has been suggested that the complex viscosity data measured by shear rheometer could be correlated to those calculated using DMA for amorphous materials (Isreb, 2011). The correlation is built on the assumption that amorphous polymers will flow below their glass transition temperature given a long enough time frame. This offers an insight into the overall behaviour of the film in terms of its response to shear forces. This could be valuable in

understanding the performance of the film during coating as well as compression at room temperature. Therefore, it was decided in this chapter to investigate the correlation between the two instruments (DMA and Shear Rheometer) in order to use the data from DMA to predict the performance of the film under various compression conditions. The previous work was carried out using the dual cantilever clamp of the DMA. While this clamp is easier to operate, it is not easily comparable to shear rheometer. The force in dual cantilever clamp is a mixture of shearing, compression and bending forces. Therefore it was decided in this work to use the tensile clamp to measure the tensile moduli. It is easier in theory to correlate between the tensile moduli of the DMA with the shear moduli of the shear rheometer. It is estimated that the tensile strength of a material is roughly three times higher than its shear elastic moduli (Mezger, 2006).

Two sets of samples of free films were analysed using shear rheometer and DMA to evaluate the behaviour of the coating polymer below and above its glass transition temperature (Tg). The possibility of fitting the DMA and PPSR results in a master curve was investigated.

4.3 Power law parameters

Polymers can typically be described by the power-law coefficient, in which a simple relationship is derived from the shear rate/viscosity curves at different temperatures. In this research work power law parameters were employed to compare the obtained results from the DMA and shear rheology results.

The general equation for a power law relationship can be written as (Larson, 1999):

$$\eta = K\gamma^{n-1} \qquad \text{(equation 4-2)}$$

Where:

η = Complex viscosity of the polymer

K = Consistency coefficient

γ = Shear rate

n = Power Law Index

n value is indirectly related to the shear sensitivity; i.e. Low n value, indicates high shear sensitivity. Shear sensitive material means that the value of the viscosity for that material changes dramatically by changing the shear rate. Consistency coefficient refers to the average of complex viscosity at shear rate of 1.

Using power law index makes it easier to compare between two different materials because it uses two parameters to describe the behaviour of the sample.

It was reported that Hypromellose acetate succinate exhibited power law behaviour over the whole temperature range of 0-130^{o}C, therefore this work investigated the possibility that ethyl cellulose (another cellulose derivative) exhibit similar behaviour (Isreb, 2011).

4.4 Results

In this chapter the linear viscoelastic range (LVE) of the coating polymer, complex viscosity and the relaxation times were studied and discussed

4.4.1 Rheological measurements of the coating polymer using PPSR

Samples of the coating films were tested and the viscoelasticity of the melt polymer above its Tg value was determined as shown in details in section 2.2.6

4.4.1.1 Determination of the linear viscoelastic region using the amplitude sweep test

The amplitude sweep test is an oscillatory test carried out at variable amplitudes (or strains) at constant frequency and temperature. The amplitude is the maximum of the oscillatory motion. For the analysis the storage modulus G' and the loss modulus G'' are plotted against the amplitude of the strain at a constant frequency. At low deformation G' and G'' are constant; the sample structure is undisturbed. This type of behaviour is known as linear viscoelastic behaviour and the extent to which this is true is known as the linear viscoelastic regime (LVE). When the amplitude value increases above that region the structure of the sample is irreversibly damaged and the values of the moduli starts to decrease. The plateau value of G' in the LVE region describes the rigidity of the sample at rest whereas the plateau value G'' is a measure of the 'flowability' of the unsheared sample. The ratio of the G' and G'' provides further information characteristic

of the sample: if the storage modulus is larger than the loss modulus - the sample behaves more like a viscoelastic solid. On the other hand, if loss modulus larger than storage modulus in the LVE region, the sample has viscoelastic properties of fluid. This ratio is known as tan delta.

Amplitude sweep testing can also determine the yield point of the material at a particular temperature. Hence two characteristic parameters can be determined from these tests: the

extent of the LVE region and the intersection of the G' and G'' curves (yield point) (Mezger, 2006)

Figure 4-1 demonstrates that the maximum value of the LVE range of ethylcellulose coating film with 30% TEC is around 10% at 120 °C and around 5% at 120 °C. In figure 4-2 the behaviour of a sample of ethylcellulose coating film plasticized with 20% TEC and analyzed at 140 °C is shown, it is clear that the crossing point between loss and storage moduli was about 3% at 140 °C. For this reason a value of 1% strain amplitude was used to analyze the entire samples during the frequency sweep tests (these must be performed within the LVE).

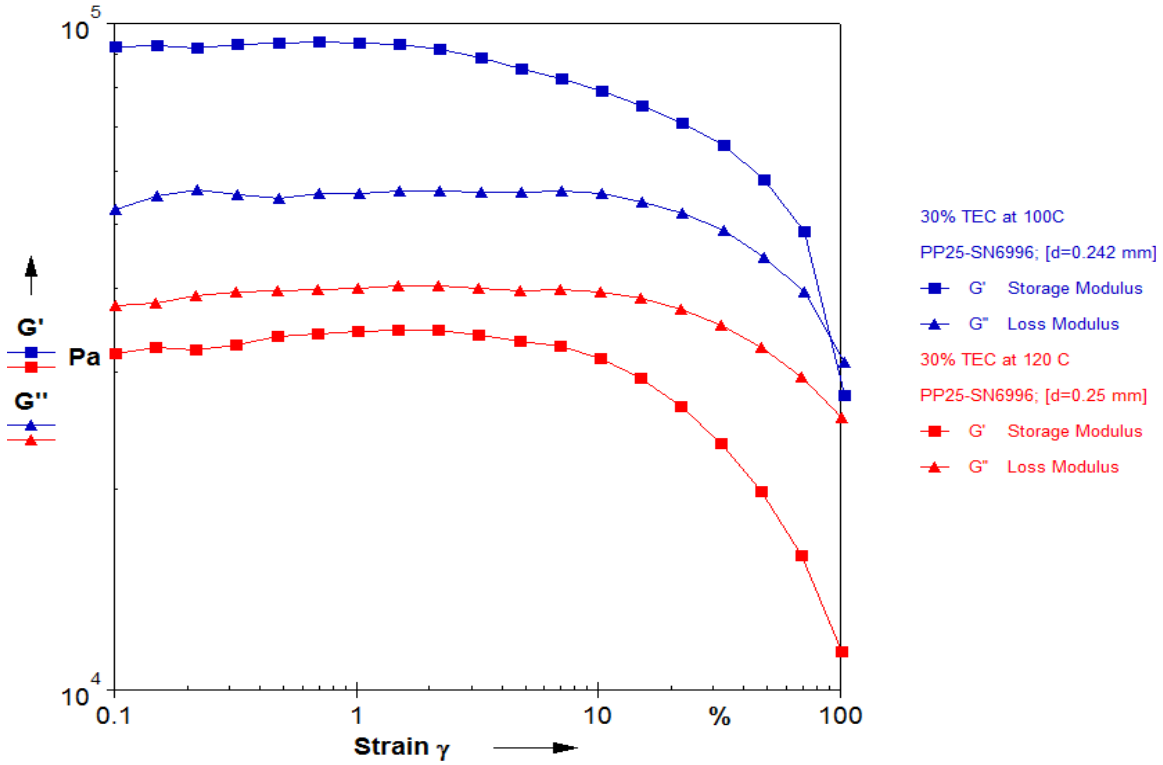

Figure 4-1: strain amplitude sweep test for ethylcellulose coating film with 30% TEC at 100 and 120 C°

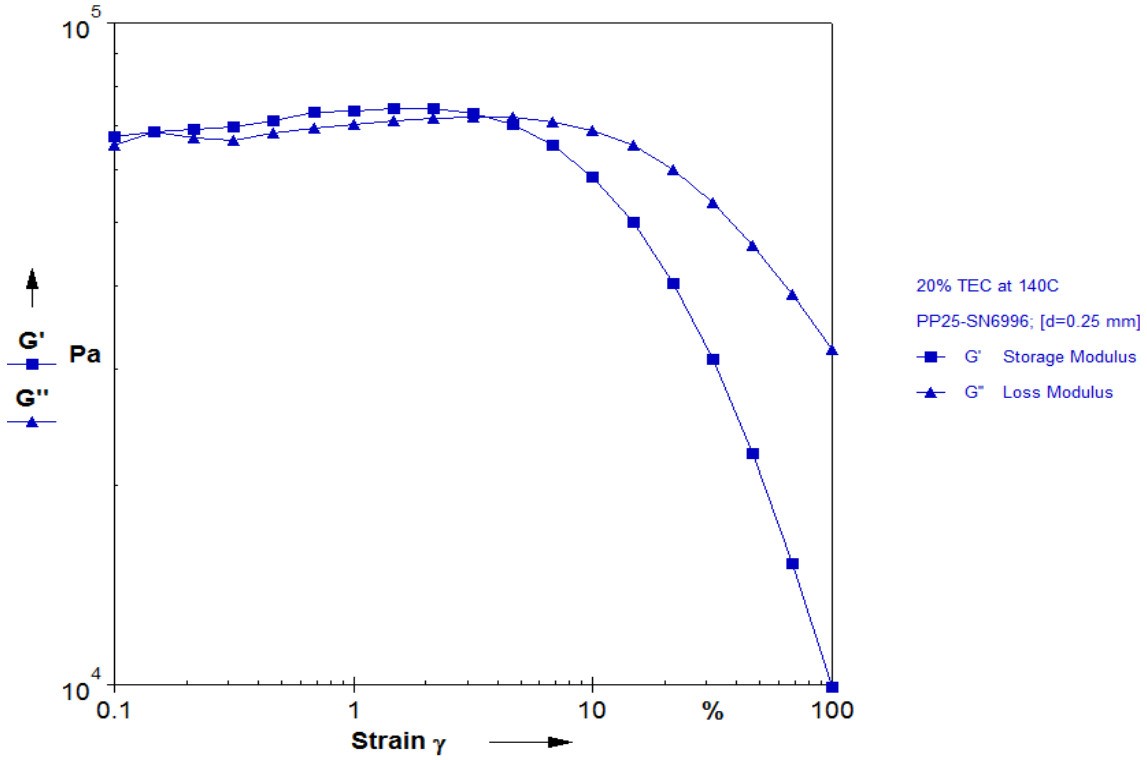

Figure 4-2: strain amplitude sweep test for ethylcellulose coating film with 20% TEC at 140 C°

4.4.1.2 Determination of the complex viscosity using frequency sweep test

In this test the samples were subjected to variable frequency of oscillation while the amplitude of the deformation - or strain is kept constant below the LVR limit. The frequency sweep test in oscillatory mode was used to estimate the complex viscosity of pure coating film and plasticized films. Both loss and storage moduli were obtained from the frequency sweep tests from which the complex viscosity was calculated.

Figures 4-3 to 4-5 illustrate the loss, storage moduli and complex viscosity for each film sample under different temperatures. From the figures it is clear that the values of loss modulus, storage modulus and complex viscosity decreases by elevating the temperature. The only exception to this trend are the films plasticised with 30% PEG at temperature higher than 110 C° this could be due to the phase separations in these films

From the figures, it can be seen that the cross-over points of the storage and loss moduli are shifting to higher frequency as the temperature increases. This is to be expected according to the time-temperature superposition principle (Larson 1999). However, The storage and loss moduli continue to run parallel to each other after the cross over point.

As discussed previously in section 1.12.14, The cross-over does not indicate the beginning of terminal relaxation phase (phase D) instead it seems that the storage and loss moduli are staying parallel and crossing each other more than once. This is indicate that the polymer is not fully relaxing even

when it is heavily plasticised. Moreover, there is no dominant elastic nor viscous behaviour at any frequency within the tested range (Larson 1999)

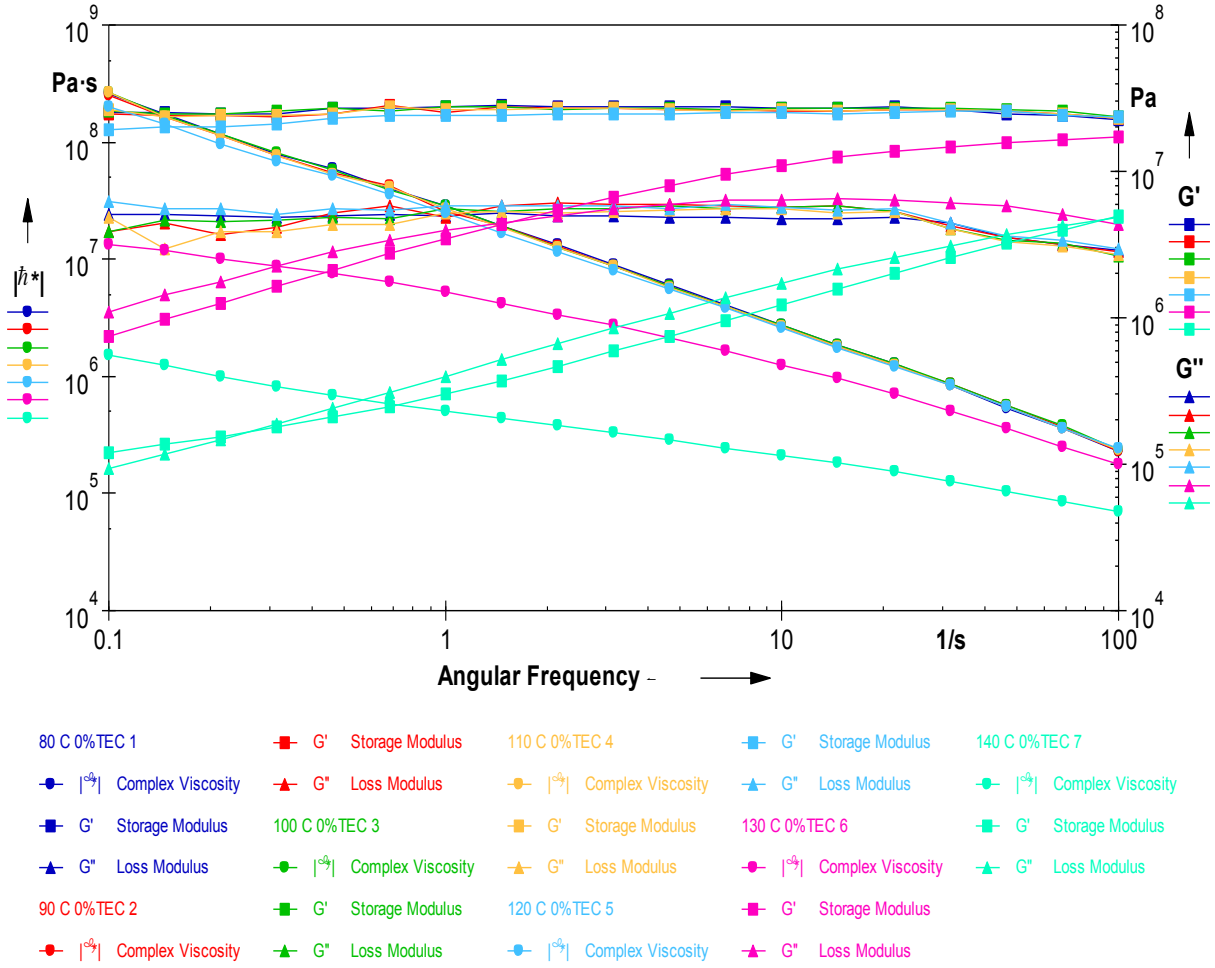

Figure 4-3: Frequency sweep tests of ethyl cellulose coating film without plasticizer at different temperatures

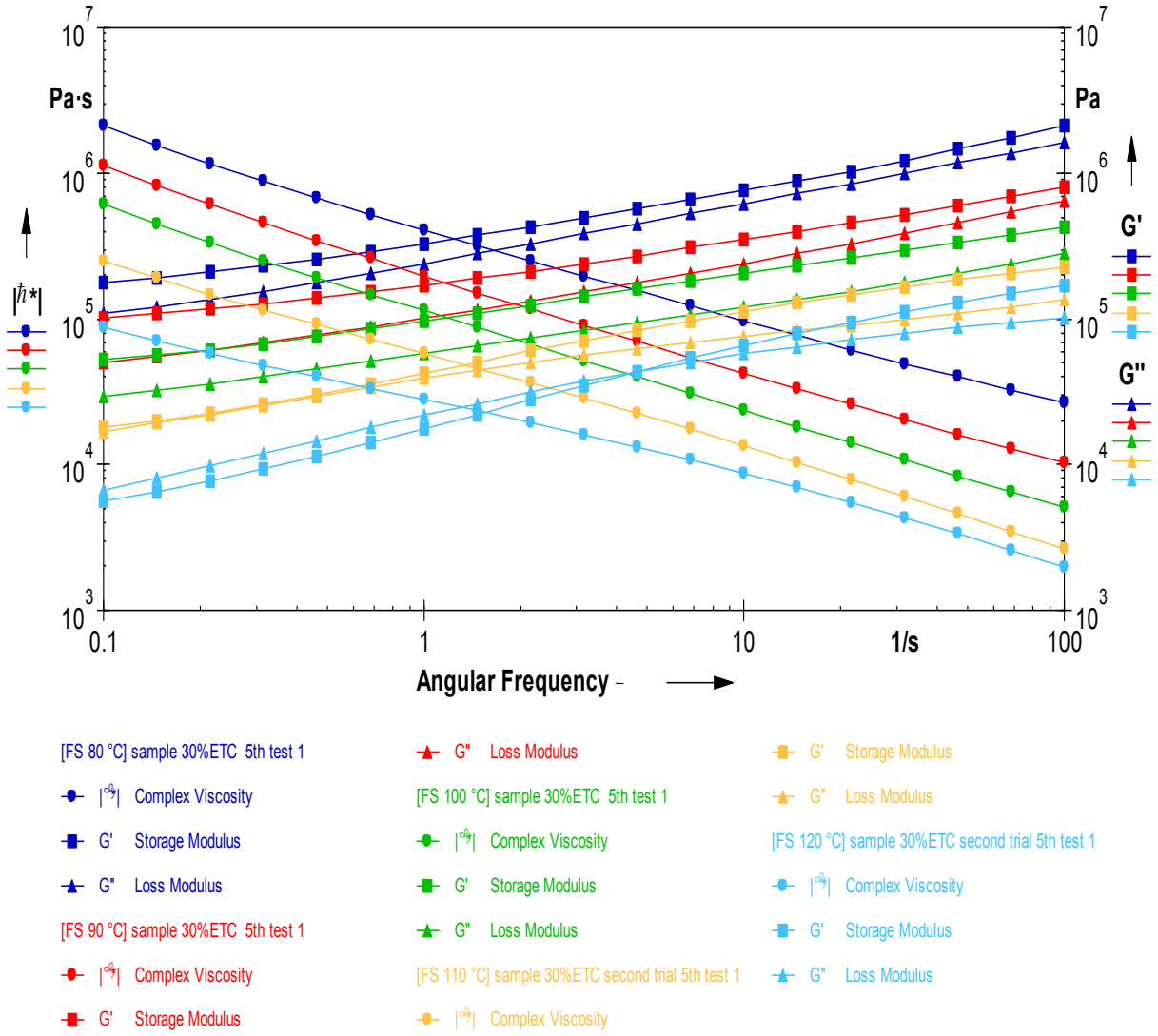

Figure 4-4: Frequency sweep tests of ethyl cellulose coating film plasticised with 30% TEC at different temperatures

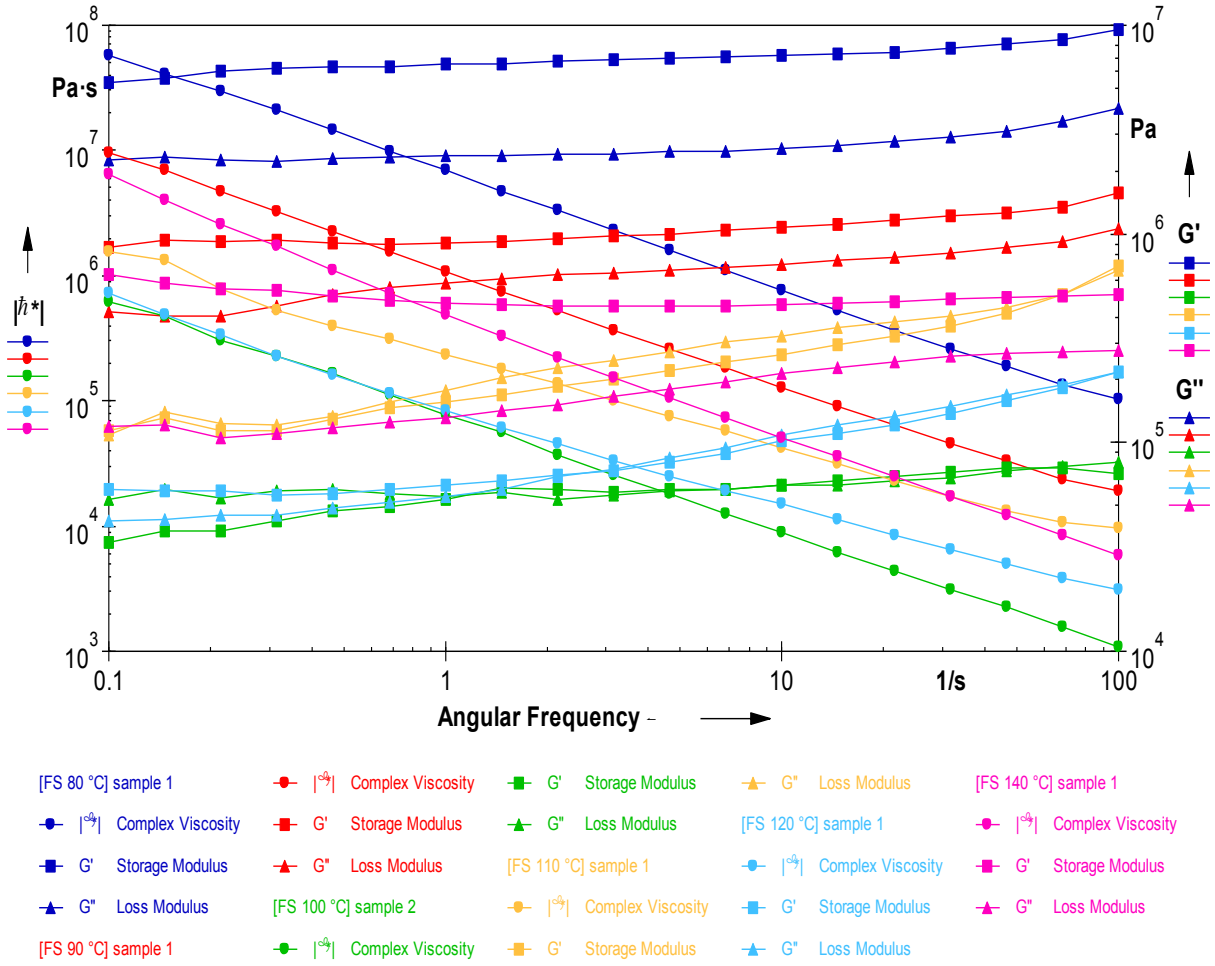

Figure 4-5: Frequency sweep tests of ethyl cellulose coating film plasticised with 30% PEG400 at different temperatures

4.4.2 Oscillation test in DMA

In this section, the oscillation test results in the DMA were conducted in order to compare the obtained results with the shear rheometer results. The same structure of analysis was followed as in shear rheometer. Therefore, the linear viscoelastic region was determined using strain sweep test and then followed by frequency test within the identified strain value.

4.4.2.1 Strain sweep test in DMA

As discussed in Chapter 2, DMA was used to study the mechanical properties of the coating film. Figures 4-6 it illustrates that complex viscosity, storage modulus, loss modulus, and tan delta follow similar trends with all exhibiting approximate linearity within the range from 0.1 to less than 0.3% strain. Since 0.1% strain is well within the sensitivity range of the DMA for this reason it was selected in this test

Figure 4-7 show that by increasing the temperature from 60 to 110 °C, the linear region extended because the sample at higher temperature becomes more viscous. Furthermore, samples plasticised with 30% TEC show lower complex viscosities than the non-plasticised sample as expected and in concurrence with the rheological tests previously described

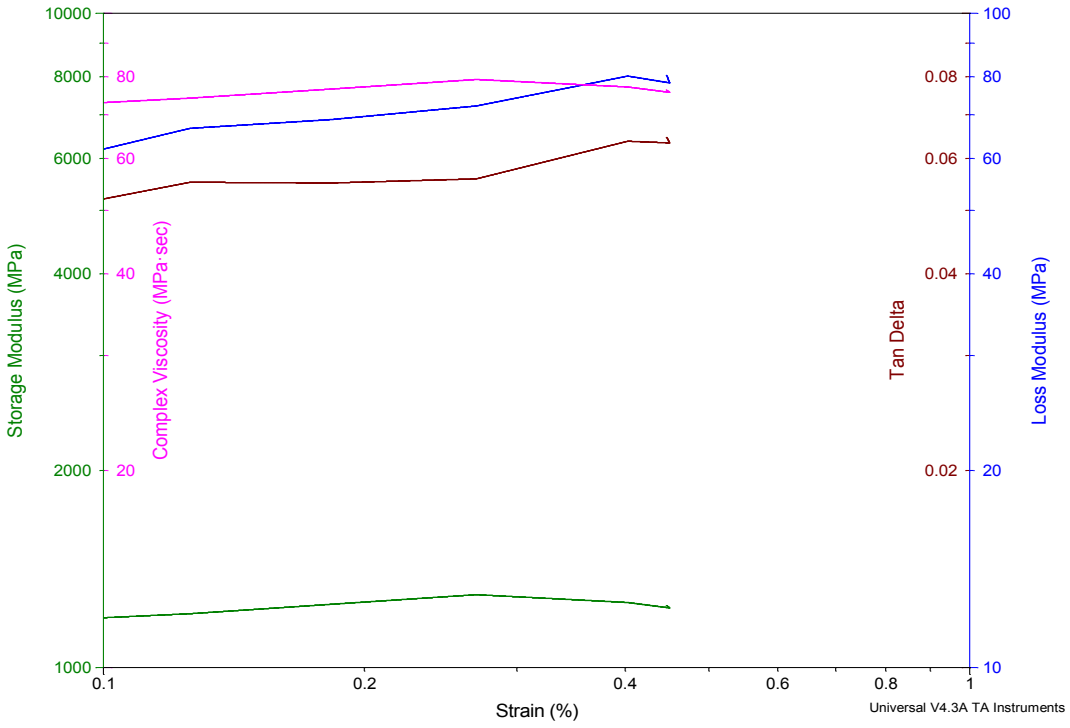

Figure 4-6 Plot of strain sweep test of pure ethylcellulose film at 60 °C

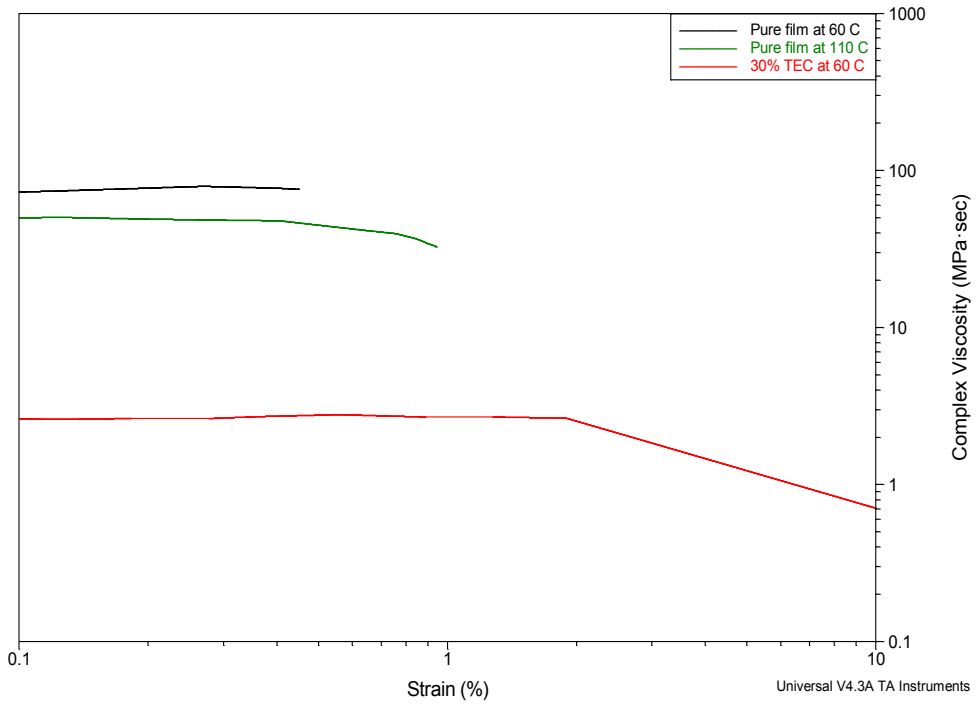

Figure 4-7 plot of strain sweep of pure film and plasticised film with 30% TEC at different temperature

4.4.2.2 Frequency sweep test in DMA

The dynamic behaviour of samples of ethyl cellulose cast film with and without plasticizers at different levels was measured using DMA. The tensile clamp was connected to the DMA and used to measure each individual sample. Both loss and storage moduli were measured at temperature ranges above and below the Tg of each film sample (as determined by DSC). Further results obtained by calculation were tan delta, (equivalent) angular frequency and complex viscosity. Figure 4-8, illustrates the complex viscosity behaviour of the pure film sample of ethyl cellulose over a temperature range from 40 to 120^{o}C. The sample has a very high complex viscosity.

By increasing the level of TEC as plasticizer from 10 to 20% w/w TEC, the plots start to spread out from each other as the sample is plasticised and the temperature crosses over the Tg value. As a result of this the complex viscosity reduces rapidly as shown in figure 4-9 and 4-10. The same trend was observed during testing using different levels PEG400 as shown on the appendices of this thesis.

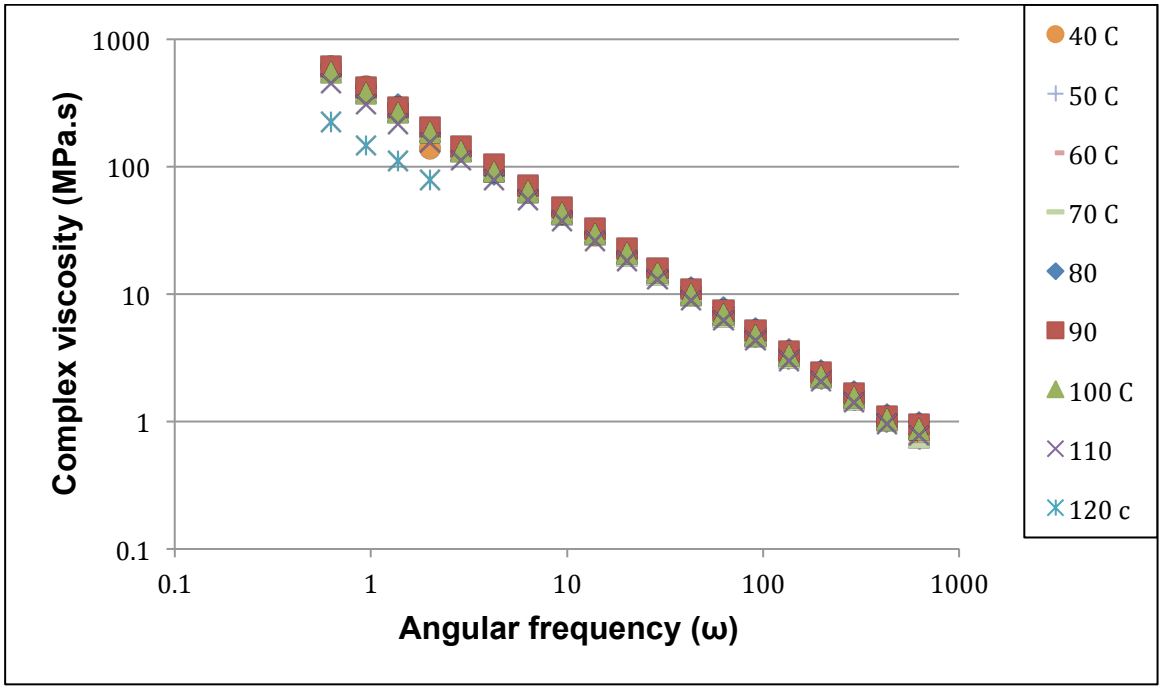

Figure 4-8 Plot of DMA for Complex viscosity against angular frequency of pure ethyl cellulose cast film at 40 to 120 °C

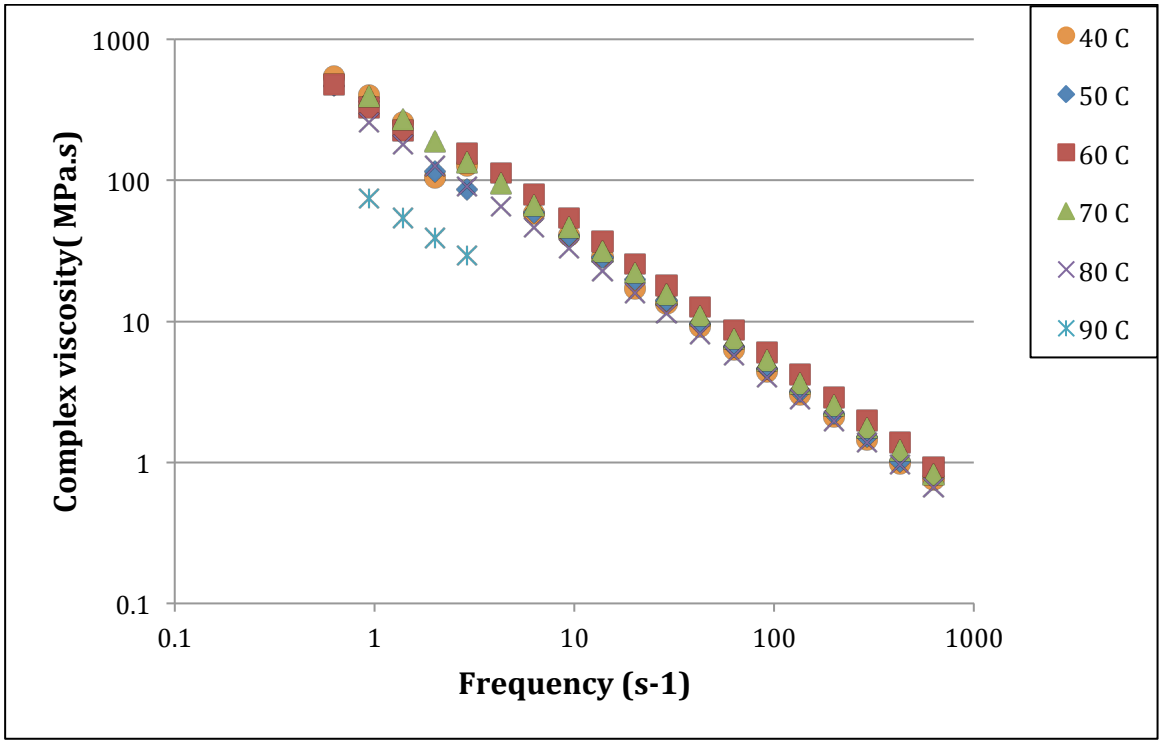

Figure 4-9 Plot of DMA for Complex viscosity against angular frequency of ethyl cellulose cast film plasticized with 10%TEC at 40 to 90 °C

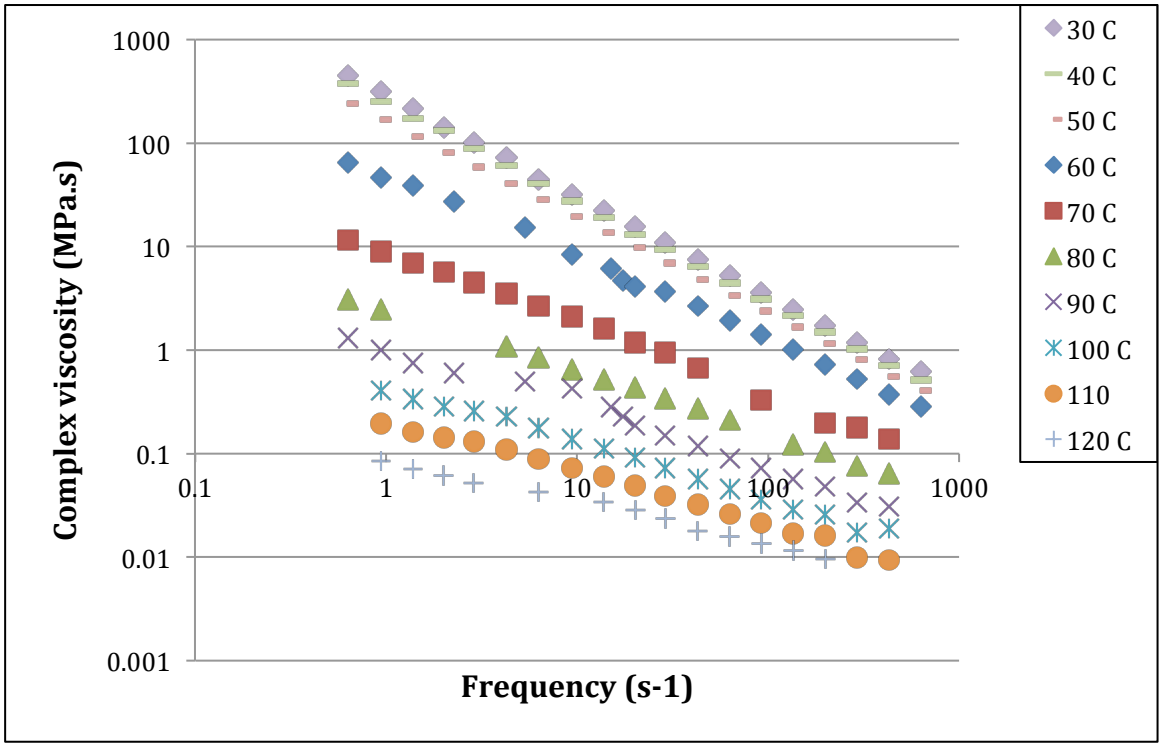

Figure 4-10 Plot of DMA for Complex viscosity against angular frequency of ethyl cellulose cast film plasticized with 20%TEC at 30 to 120 °C

4.4.2.3 Power law and time-temperature superposition

The principle of time-temperature superposition states that the rheological moduli of amorphous polymers (and any polymer that doesn't change its structure with time) shifts to higher frequency as the temperature increases. In other words the shape of stress-strain or elastic modulus doesn't change when temperature is increased but only shifts towards a higher frequency (or shorter time frame). This is explained by WLF equation (Painter et al 2008). This principle has many useful applications when testing a polymer behaviour at long timeframe or high frequency is not feasible. As the temperature drops below the Tg of the polymer, the localised movement of the chain may not obey the WFL equation however it should still obey simple Arrhenius equations. It was reported that HPMCAS obeyed Power law model when complex viscosity data measured by DMA and shear rheometer above and below the Tg were fitted (Isreb, 2011). In fact the complex viscosity measured by DMA using dual cantilver clamp was found to be comparable to that measured by the shear rheometer without using any correlation factor (Isreb, 2011). It would be therefore interesting to find out the correlation between the tensile clamp and the shear rheometer. It is accepted that a simple tensile modulus is 3 times higher in value than its shear counterpart (Mezger, 2006). The power law is a typical model for shear-thinning polymers in the frequency region between the infinite and zero shear plateau.

Figures 4-11 and 4-12 show a study of the consistency coefficient of the power law of samples of free film of ethyl cellulose with or without plasticizers. The consistency coefficient is a mean value of the complex viscosity at shear

rate of 1 Hz. During this study the samples were analysed under a wide temperature range using DMA and shear rheometer. The result shows that measurements using the DMA exhibit the same trend as those obtained from the shear rheometer. Pure Ethyl cellulose films shows a difference of 10 folds between DMA and shear rheometer data. However the difference is much closer for the plasticised films

The reason for this inconsistency in the results between DMA and shear rheometer can be because the samples were measured at their limits of deformation. During analysis the samples in the shear rheometer at low temperatures are quite elastic, hence there is a high possibility of sample-plate detachment during the experiment (wall slipping) (Cloitre et al, 2017). On the other hand, during DMA analysis the sample becomes soft and 'saggy' as the temperature crosses over the Tg threshold. Hence the sample in the DMA can already be strained at Tg whereas, at the same temperature the sample in the shear rheometer conforms to the test geometry with no additional strain imposed. This has been observed in molten polymer samples when measured using using dual cantilever (Isreb 2011). However, the tensile clamp is more sensitive to samples sagging that dual cantilever. It is also more affected by cracks in the sample during preparation and there are more chances of sample slipping from the clamp than in dual cantilever. Another factor might be the high viscosity of the ethyl cellulose film making it harder to measure in the shear rheometer. It is interesting to notice that TEC 20% plasticised film showed a good correlation between DMA and shear rheometer. This film is the one with the lowest viscoelastic moduli.

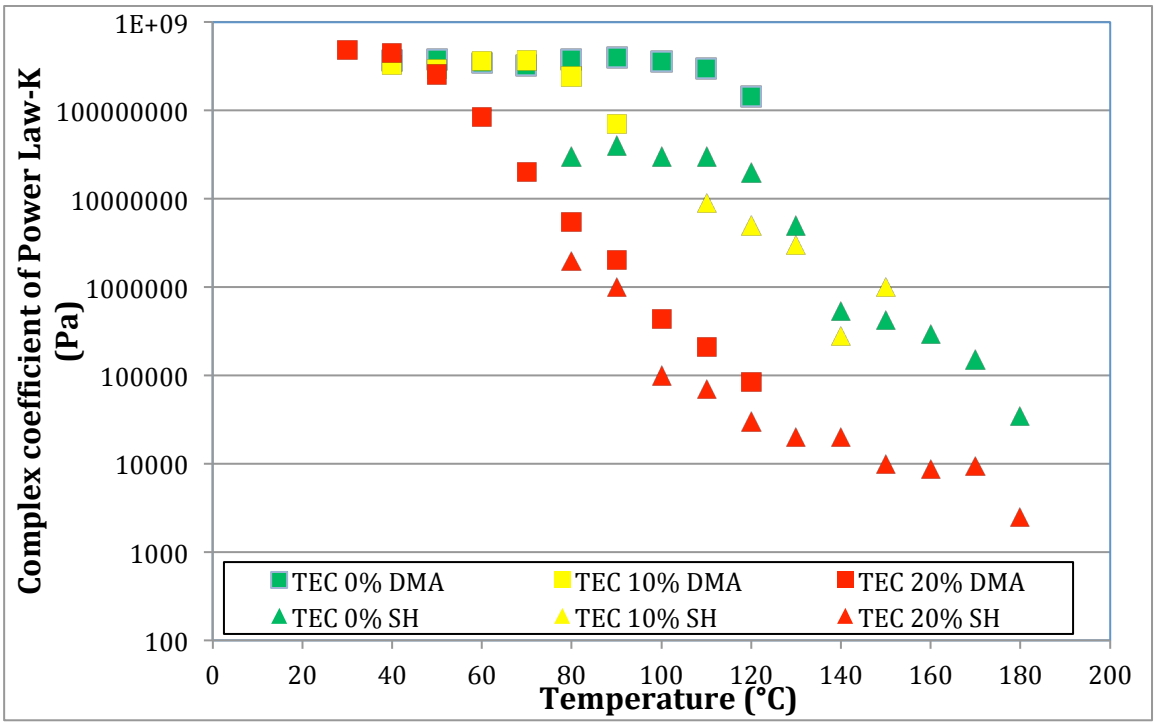

Figure 4-11 Plot of combined results obtained by DMA and Shear Rheometer (PPSR) of consistency coefficient of power law for ethyl cellulose film without and with different % w/w of TEC over range of temperature

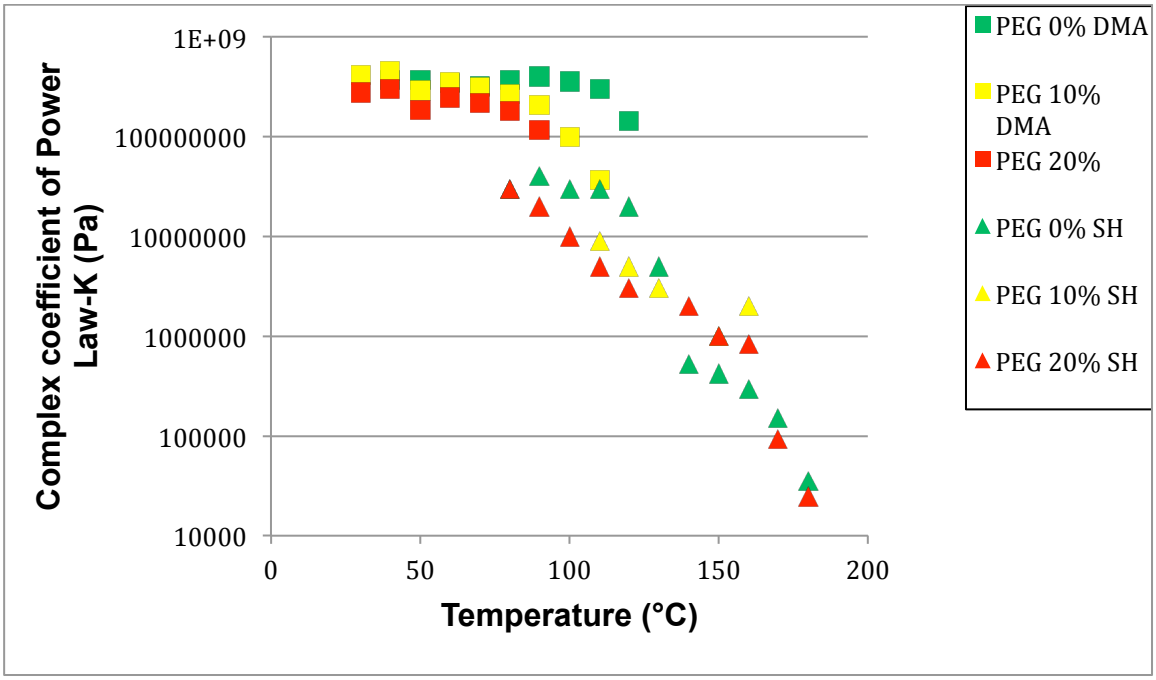

Figure 4-12 Plot of combined results obtained by DMA and Shear Rheometer (PPSR) of consistency coefficient of power law for ethyl cellulose film without and with different % w/w of TEC over range of temperature

Figure 4-13 illustrates the variation of the power law index with temperature. Under the Tg value it is clear that there is a slight increase in the power law index, while it starts increasing more dramatically after that Tg. The lower the value of power law index the more shear sensitive the material is. Therefore it is expected to see the shear sensitivity peaking around the Tg value of each film. This has been demonstrated before in HPMCAS (Isreb, 2011) and in various molecular weights of HPC (Paradkar et al, 2009)

Figure 4-13, illustrates the results obtained from DMA and PPSR are following similar trends. The difference between the values measured in DMA and shear rheometer however is more consistent but still significant. This can be explained in a similar fashion as in the previous two figures.

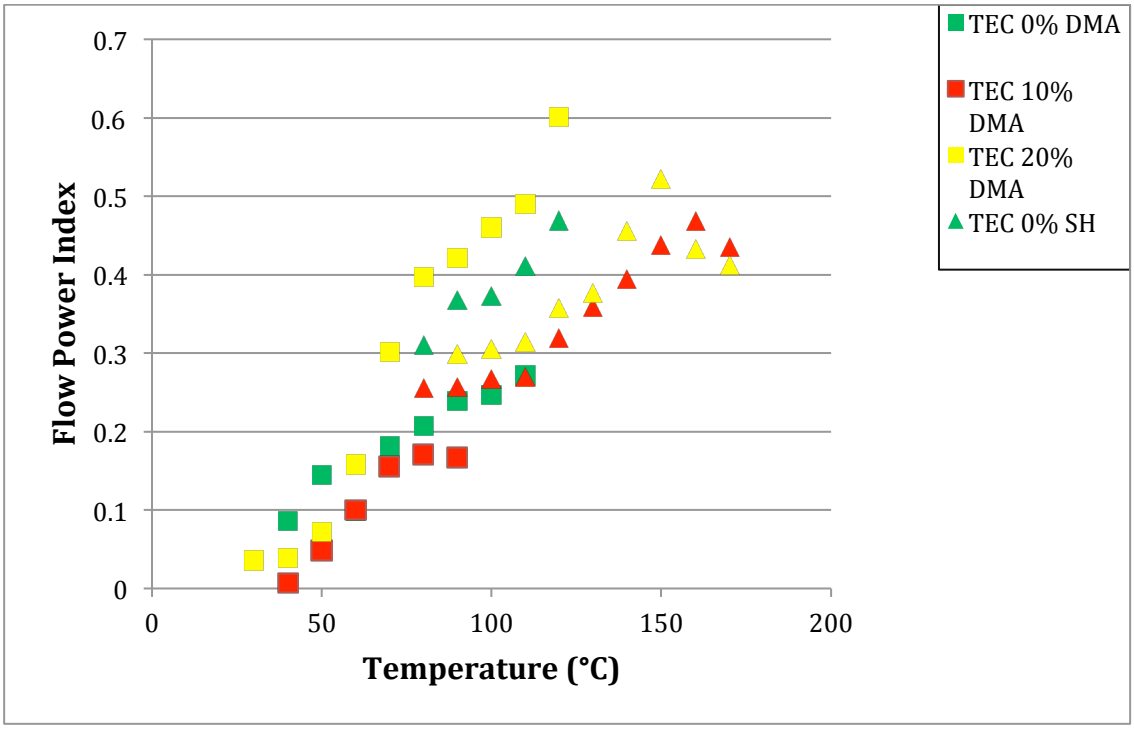

Figure 4-13 Plot of Power Law Index of ethyl cellulose film without and with different % of TEC measured by DMA and Shear Rheometer (PPRS)

4.5 Conclusion

DMA and shear rheometer in attempt to understand the behaviour of the film during coating and during compression of the coated pellets. The study attempted to produce a continuous master curve for the behaviour of non plasticised and plasticised films under various shearing rates and temperature. DMA and shear rheometer were used to produce the complex viscosity data. From the figures presented it is clear that the values of loss modulus, storage modulus and complex viscosity decrease by increasing the temperature. The curves indicate crossing points of loss and storage moduli in different shear rate ranges. A horizontal shift to the cross-over points was very clear in different experiments (time-temperature superposition). At temperatures higher than the Tg value, both pure and plasticized coating films do not exhibit obvious viscous behaviour instead seeming to transform from predominantly elastic behaviour to weak gel-like structures (i.e., equivalent viscous and elastic moduli). Increasing the level of plasticizer from 0% to 30% did not significantly change the shape of the curves of complex viscosity, storage and loss moduli and the zero shear viscosity had not been reached by the lowest shear rate applied during testing. All plasticised films reveal smaller values of storage and loss modulus than non-plasticized films. Moreover, it is clear that both storage and loss moduli behave similarly qualitatively and quantitatively. In the PPSR graphs, it was clear that there were many cross-over points between the storage and loss modulus, nevertheless. The graphs of complex viscosity fit with power law behaviour as the material above its Tg is on the edge between a gel-like and liquid state.

DMA analysis, in tensile mode, was used to characterise the films below the Tg. The pure sample (with no plasticizers) exhibited a very high and almost constant complex viscosity due to the rigidity of the sample. The elastic component was dominant in most of the samples as the values of tan delta for most of the samples were less than unity. Also, from the result it was obvious that increasing the frequency leads to decrease tan delta

The shear thinning of the coating film can explain the viscoelasticity behaviours of the coating film. The shear thinning below the Tg of the coating polymer was more noticeable than over the Tg. The results confirm the hypothesis of that a coating polymer below its Tg behaves like a heavily viscous liquid as proposed by Isreb et al, 2011

The values of complex viscosities from both DMA and PPSR techniques exhibit power law behaviour. The rheological moduli were strongly affected by the level of plasticizer – increasing the plasticizer concentration decreases the values of moduli. Furthermore, the complex viscosity of the coating films decreases by increasing the frequency which is a typical behaviour of a shear thinning polymer. This is in agreement with previous studies on other cellulose polymer (Isreb, 2001). TEC was clearly a stronger plasticiser than PEG. 20% TEC had the lowest complex viscosity values over the whole measured temperature range

The results of the complex viscosity obtained from both DMA and PPSR followed the same trend. The non plasticized polymer showed a 10 time higher complex viscosity values when measured by DMA over that measured

by PPSR. The difference was smaller in plasticized films but it was not consistent. Therefore a consistent coefficient to correlate the DMA and PPSR couldn't be accurately determined. This might mean there is no correlation but most likely it is due to the errors in measurements in both devices. The tensile clamp is specifically very fiddly and might not be as sensitive as the dual cantilever which was used in previous studies. However the trend could be used as an evidence to the usefulness of this technique and to indicate that the oscillatory data below the Tg could still be used for comparison between the various formulations. The elasticity of the films in general might make it difficult to differentiate between the behaviour of the various formulations under compression. The next chapter will look at the effect of various compression parameters and their effect on the release of the drug.

Chapter 5

Coating, compacting of pellets and dissolution studies

5. Chapter 5: Experimental design and statistical analysis to evaluate the processing variables in MUPs production

5.1 Introduction

With the increasing interest in quality by design approach in the pharmaceutical industry, it is imperative to understand the key process and formulation parameters affecting the critical quality attributes of the products. The formulation development process can be time, materials, and efforts consuming. The recent formulation optimization utilizes systematic design of experiments. Since the number of variables involved in the pharmaceutical process is an important element, the formulation design could become part of complex statistics requiring artificial intelligence (Landin et al., 2009) (Singh et al., 2004) (Singh et al., 2005)

Factorial design has been used to evaluate the processing factors that might affect, and to optimize the pharmaceutical processes. Some of these studies are available in the public domain and many have been kept private by pharmaceutical companies. experimental design approach has proven to be very useful tool for fast and reliable formulation design (Landin et al., 2009).

(Rottähuser et Al, 1997) used the central composite design to study the effects of lubricants and compression force on the physical characteristics of effervescent tablets. It was found that using the central composite design is a successful way to evaluate the effects of variables and process parameters in the formulation development of effervescent tablet.

5.2 Chapter outlines and aims

The compression of pellets into MUPs should not affect the integrity of functional coating present on the surface of the individual pellet. This is vital to maintain the products key functions: such as be the release kinetics, taste masking, gastric resistance or drug stability. Both formulation and process parameters could be adjusted to realise this goad. The formulation approaches can be divided into three categories (Reddy, 2011): Adjustment to cushioning agents, adjustment to the pellets and adjustment of the coat. Beckert et al. demonstrated that increasing the thickness of the enteric coat can be used as a strategy to main the gastric resistance after compression (1996). Moreover, increasing the plasticizer level was found to be useful in resisting film rupture during compression (Debregeas et al., 2000). Compression force and speed were also found to affect the release profile (Bodmeier 1997). However, there is a lack of a systematic approach in the literature to investigate these key parameters and their interaction

The main goal of this chapter was to evaluate the effect of key process and formulation parameters on the quality attributes of compressed pellets of theophylline coated with ethylcellulose film. Coating level, compression force and dwell time were chosen in this study in an effort to eliminate the need for cushioning agent. The percentage of drug release was selected as the response drug release, as shown on figure 5-1.

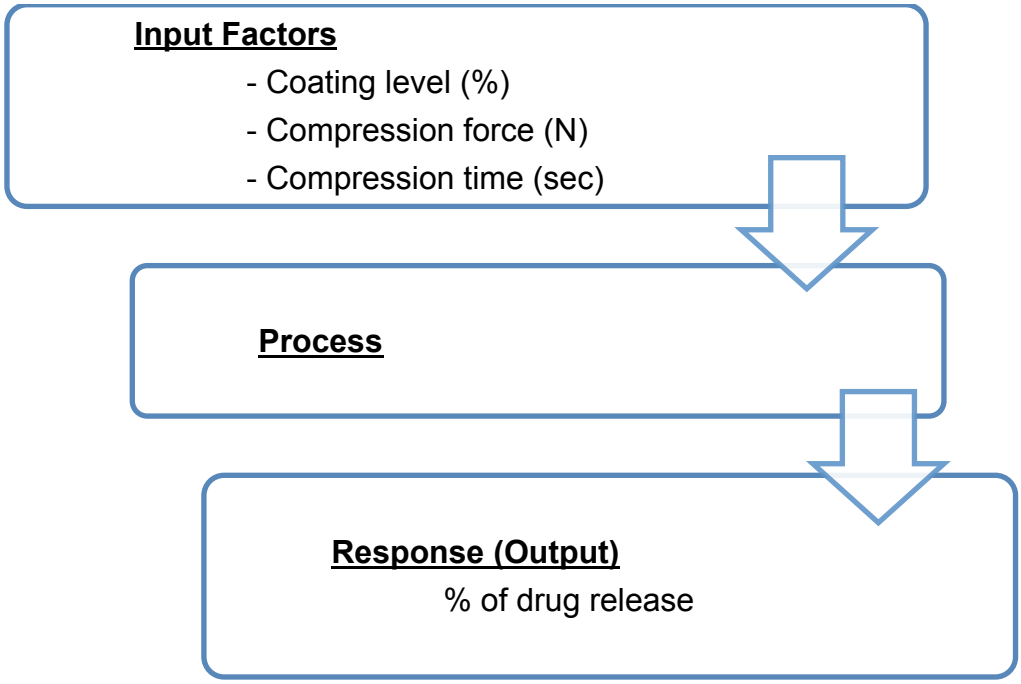

Figure 5-1: The main components of statistical analysis

In this research work Minitab statistical analysis software, version 16 was used to design the experiments and also to study the relationships between the inputs (X axis) and the output (Y axis). Minitab offers three different designs for experiments:

1. Response surface design: it is a controlled experiment including quadratic terms to model the relationship between X and Y
2. Central composite: it is a type of Response Surface design, more specifically includes a factorial block, an axial block and centre points
3. Face centred with 4 points: it is a type of central composite design. It means the axial points are 1 coded unit away from the centre points with three factors as shown in figure 5-2

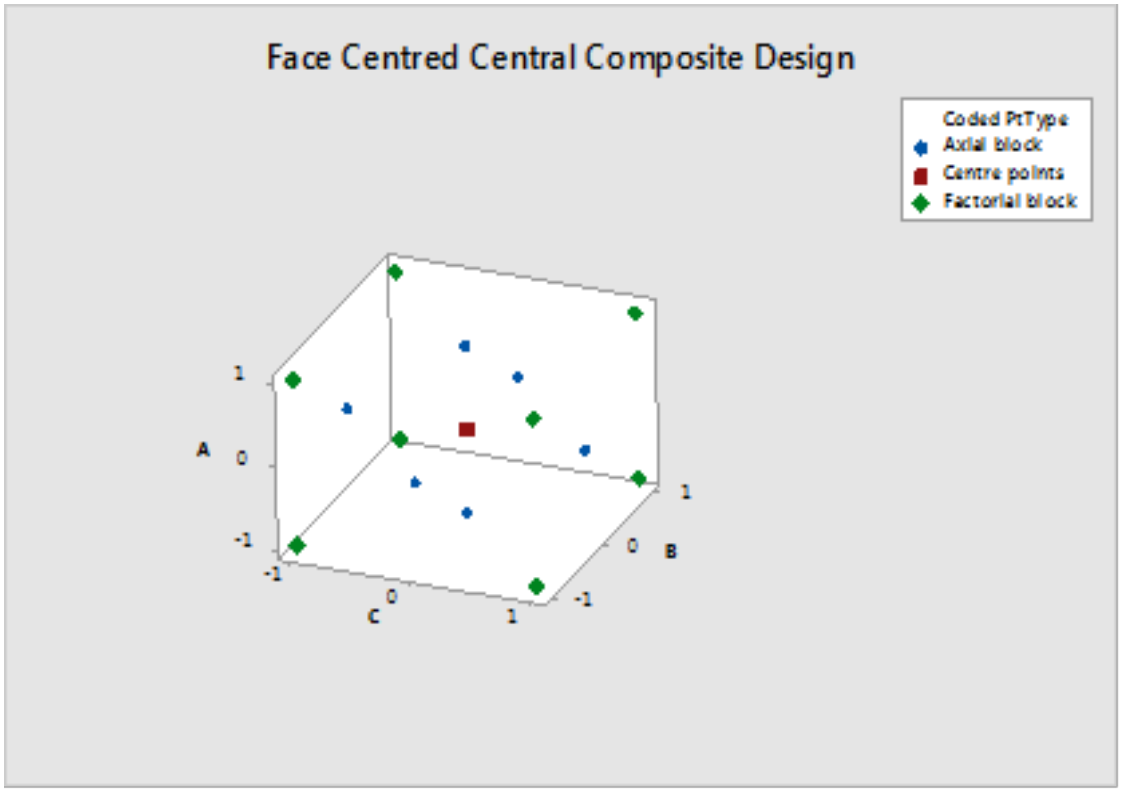

Figure 5-2: Face-Centred Central Composite Design

5.3 Results and discussion

In this section, each of the following was observed and studied: Coating process, SEM images were collected to observe the morphology of the coated pellets, and the dissolution studies were carried out in order to estimate the kinetic profile of the final product.

5.3.1 Coating process parameters

As explained in section 2.2.9, Batches of 30 g of pellets were coated using Caleva Mini Coater. Using largeer batches generated electrostatic charges (in our preliminary experiments) and this made it hard to achieve good coating consistency.

Theophylline was used as a model drug. The coating polymer was ethyl cellulose. in ethanol (10% w/w). All the parameters of the coating process have been mentioned previously in chapter 2. The drying air temperature was very critical parameter and all the coating experiments were performed at 28 °C. When drying temperature was over 30 °C, the electrostatic charges on the pellets' surfaces increased leading to twinning or agglomeration of the pellets. While using a temperature lower than 25 °C caused a wet mass agglomeration and twinning.

5.3.2 Direct compression of uncoated and coated pellets

A weight of 200 mg uncoated and coated pellets of theophylline were tabletted individually using compaction studies press from Caleva Co., as explained in section 2.2.10

This research work focused on the effect of processing parameters such as compression force, dwell time and the level of coating (% w/w) on the kinetic

profile. The internal relationships between those parameters were investigated. Minitab 16 software, for statistical analysis initially was used to design the experiments. In this research work both central composite and factorial design were used. The experiments were designed by the central composite design, which is a response surface design that allows us to model the quadratic relationship between the inputs and output. Although the experiments were designed by central composite design, the factorial design was used to analyse all the experiment because factorial design analyse the linear or proportional relationship between the inputs (coating level, compression force and compression time) and the output (dissolution).

The suggested experiments were based on the factorial 2 level design, central composite (which means low setting, high setting and central point in between the two settings), face centred with four points, to study the relationship between those factors. Table 5-1, demonstrates the experimental design suggested by Minitab 16. In order to ensure the reproducibility all the runs were repeated in duplicate.

Table 5-1: The suggested experimental design using different coating level, compression force and compression time using Minitab software

Run Order	Coating level (%)	Compression force (N)	Compression time (sec)
1	7.5	7000	0.1
2	2.5	7000	1
3	2.5	7000	0.1
4	2.5	3000	1
5	5	5000	0.55
6	7.5	3000	0.1
7	2.5	3000	0.1
8	5	5000	0.55
9	7.5	7000	1
10	7.5	3000	1
11	2.5	5000	0.55
12	7.5	5000	0.55
13	5	3000	0.55
14	5	7000	0.55
15	5	5000	0.1
16	5	5000	1
17	5	5000	0.55
18	5	5000	0.55

5.3.3 SEM images of coated pellets compressed at different compression forces

The nature of deformation of ethyl cellulose coating film under different compression force and different coat loading was investigated. The impact of compression force and coating level on the kinetic profile were studied. Samples of compressed pellets (tablets) were cut and then scanned using Scanning electron microscope (Oxford instrument, UK). Figures 5-3 to 5-7 reveal the influence of the coating level and compression force on the coated pellets. From these images it is clear that ethyl cellulose film is cracking under pressure, however increasing the coating load level improves the plastic deformation of the film thus reducing the breakage to the coating film. This is in agreement to what has been previously observed (Beckret et al, 1996). Also, it was noticed that the compression force has a noticeable effect on the film durability as by increasing the compression force from 3000 to 7000 N, the breakage of the film coating increased. This is also in agreement with the literature (Bashaiwoldu, 2002) The minimum breakage was noticed on films coated with 5% and compressed at 3000N (Figure 5-6).

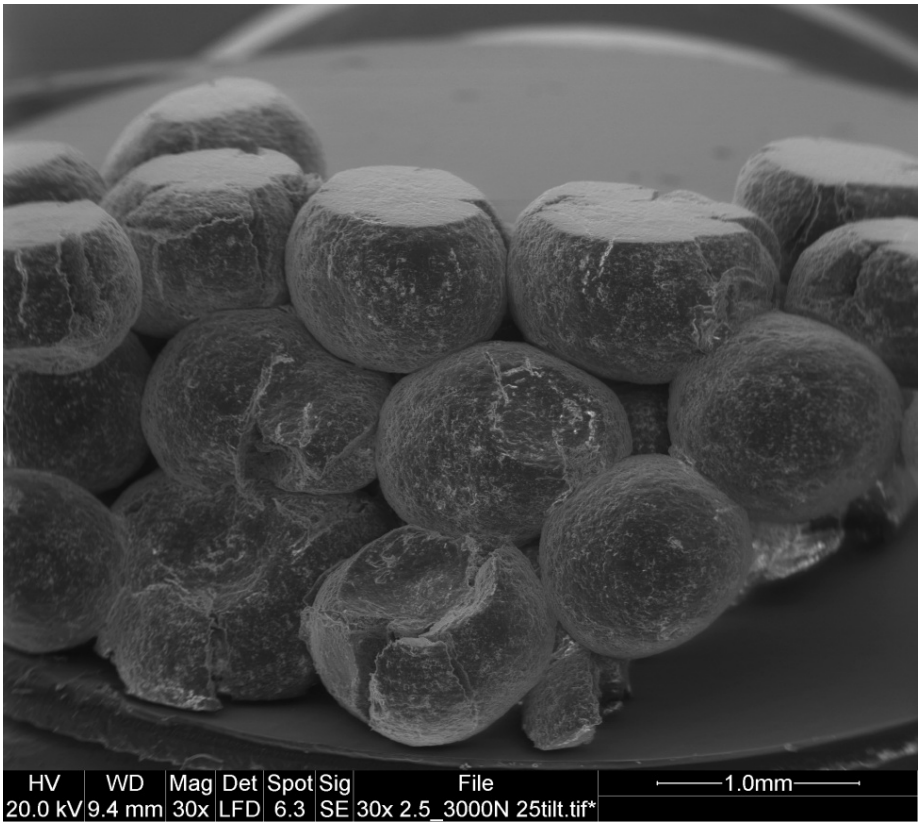

Figure 5-3: Crossed-section of with 2.5% w/w coating level and compressed at 3000 N

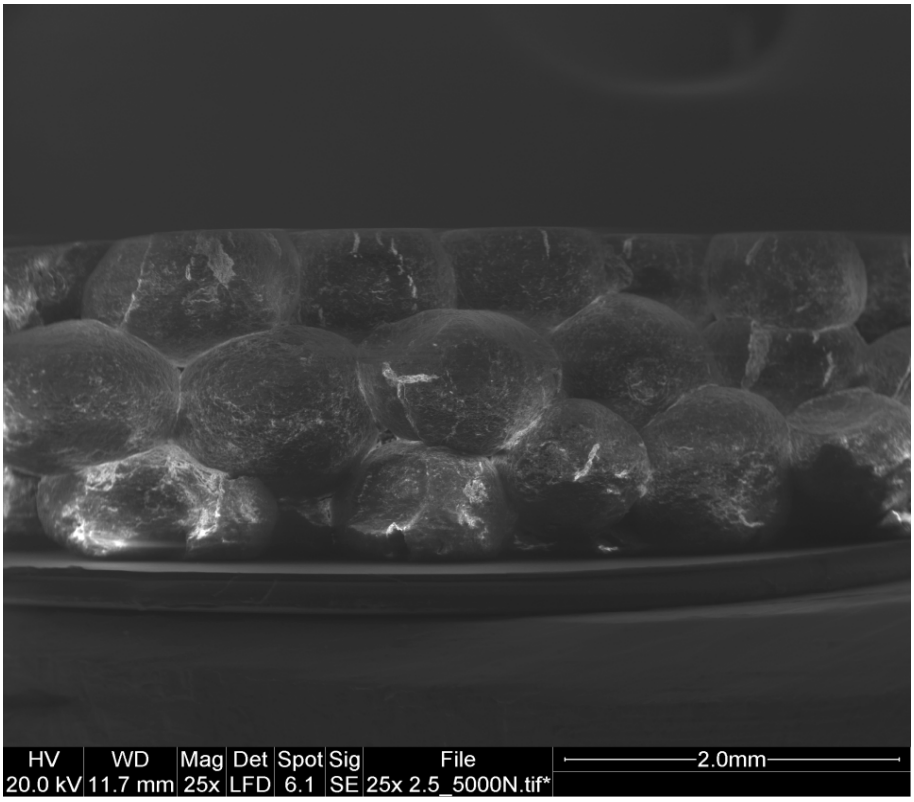

Figure 5-4: Crossed-section of with 2.5% w/w coating level and compressed at 5000 N

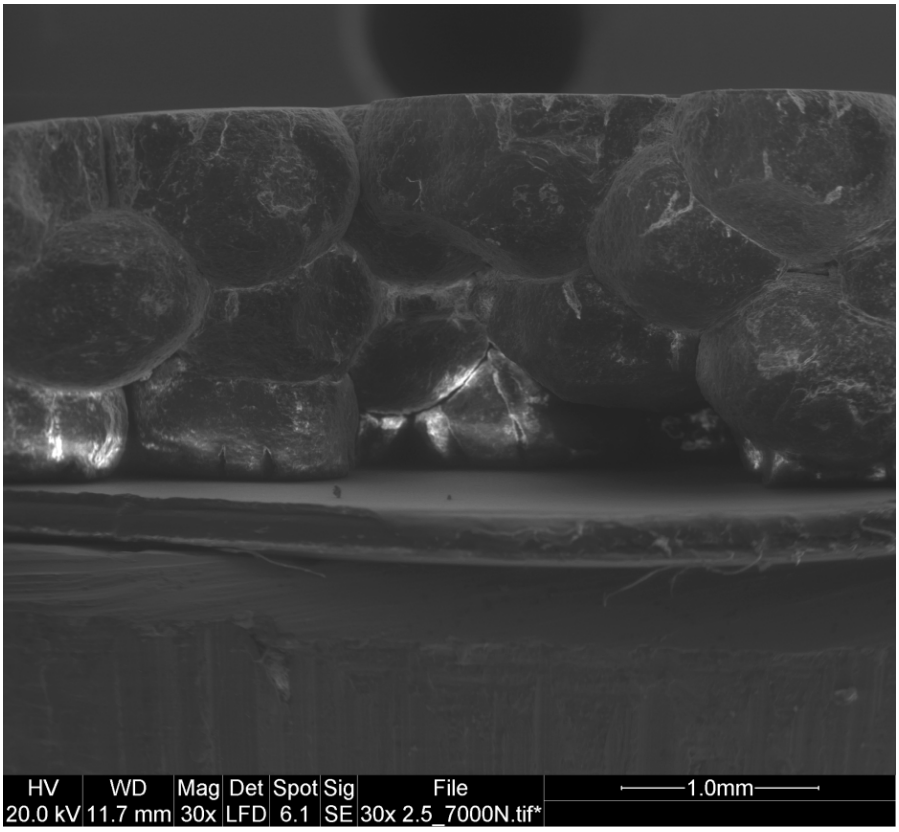

Figure 5-5: Crossed-section of with 2.5% w/w coating level and compressed at 7000 N

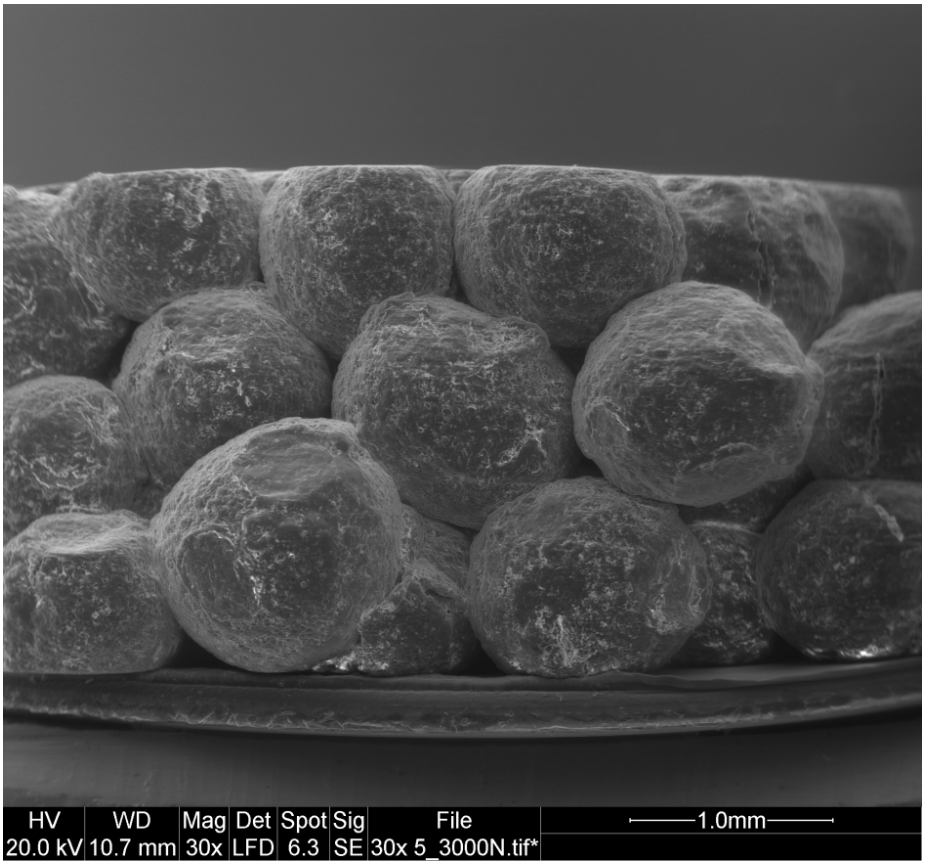

Figure 5-6: Crossed-section of with 5% w/w coating level and compressed at 3000 N

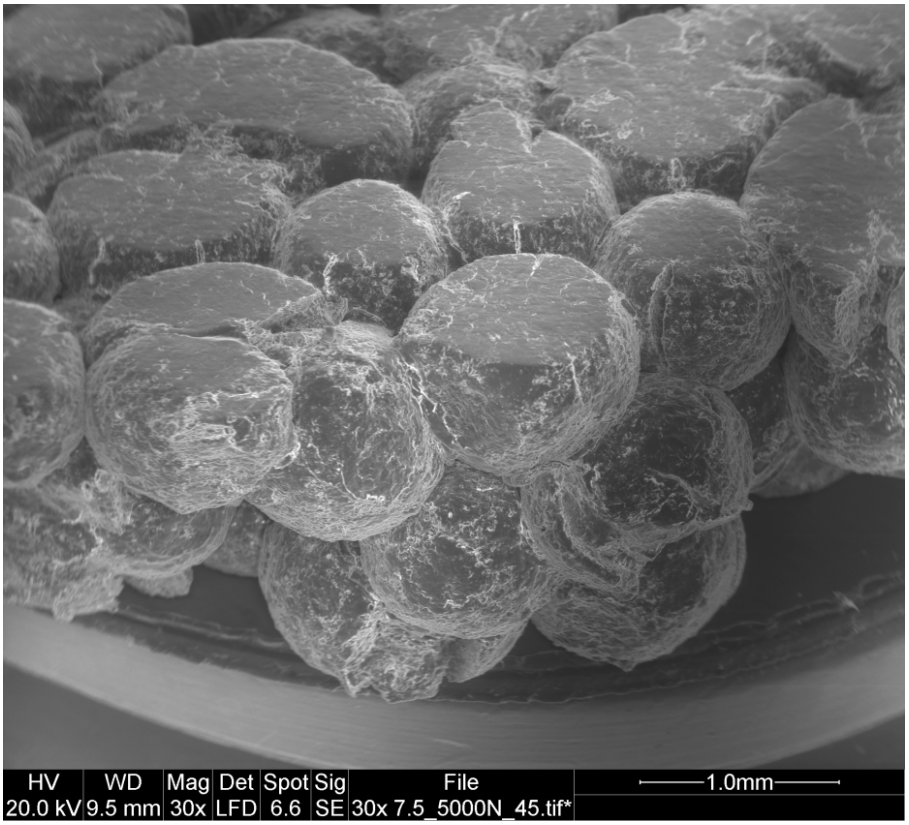

Figure 5-7: Crossed-section of with 7.5% w/w coating level and compressed at 7000 N

5.3.4 Dissolution studies of coated compressed pellets

The suggested runs using Minitab as listed in table 5-1 were evaluated by the dissolution studies.

Figure 5-8 shows the results of dissolution studies of 18 experiments of coated compressed pellet at different manufacturing parameters as shown on table 5-1. Dissolution was carried for 6 hours, and sampling time was once every 30 min for the first two hours then once every 1 hr. It was obvious that the coating level has significant effect on the percentage release. As increasing the coating level from 2.5 to 5 and then to 7.5%, caused a noticeable reduction in the percentage of release. This is in agreement to

previous literature (Sundar et al., 2017). On the other hand, the compression force has a minor effect on the percentage release which is to the contrary to what was found in previous experimental design studies (Reddy, 2018). This could be however due to the relatively weaker and brittle nature of the sugar pellets used in that study (no film coating).The dwell time has no effect on the dissolution as by increasing the dwell time from 0.1, 0.55 and 1 sec, the percentage release was not affected. This could be explained by the elastic nature of ethylcellulose which means it requires longer time to dissipate significant amount of the stored energy upon compression than those studied in this work

Figure 5-9 and 5-10; illustrate the influence of the manufacturing factors (coating level, compression force and dwell time) on the percentage release at 30 min and 6 hours of the dissolution time. Furthermore, figure 5-10 show the influence of the factors and also the interaction between those factors on the percentage release.

The red line on figure 5-10, represents critical t-statistic for a P value of 0.05. It corresponds to a key value of 0.05 and is used to test the hypothesis for the relationship between the input parameters and output. Y axis represents each factor either separately or combined with another factor to study the effect of the factors and the interaction between factors.

The P value represents the probability there is no interaction between the inputs and the output, If we have P value of 0.05 (5%) that means there is a 5% chance there is no relationship between X and Y axis.

The P value can be bigger or smaller. If smaller as 0.01 (1%) that means there is 1% risk of making wrong decision and we are more confident there is a relationship between the inputs and the outputs. For this reason it is important to obtain more data by achieving more experiments.

The bars in Figure 5-9 represent the coating level (A), compression force (B), compression time (C) and all the interactions between A, B and C. The red line represents the change that would expect to see by chance only 5% of the time. So it corresponds to the P value. It can be clearly seen that the coating level is the main factor affecting the drug release after 30 min from the coated pellets. Interestingly the effect of coating level on the release after 6 hours was less significant. This could be due to the swelling of the film in the coating media blocking the cracks that has formed (Spencer, 2007)

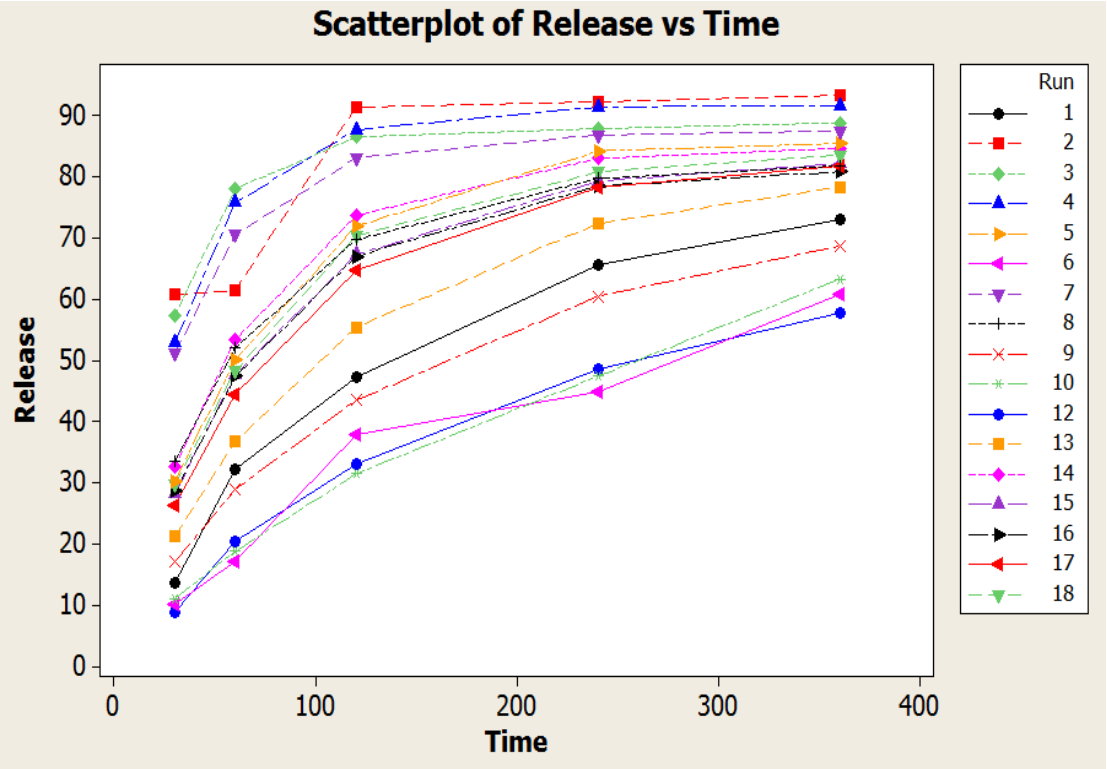

Figure 5-8: The kinetic profile for the suggested experiments using Minitab16

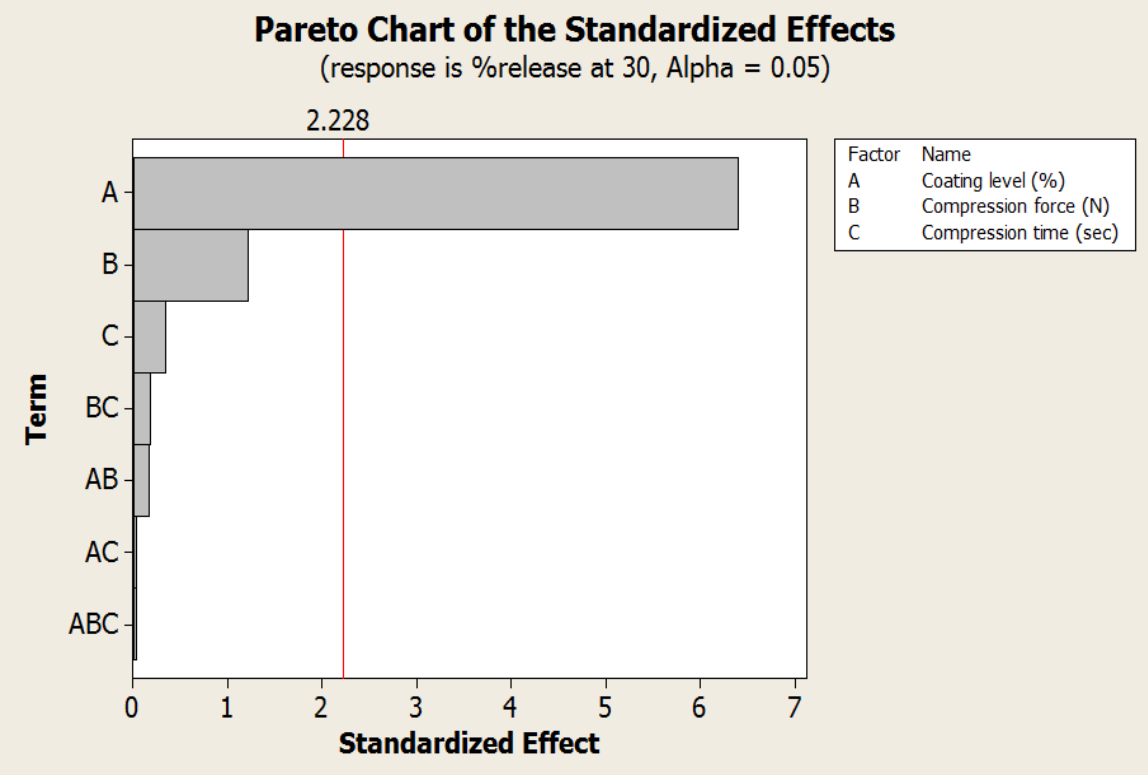

Figure 5-9: the influence the coating level, compression force and compression time on the percentage release at 30 min

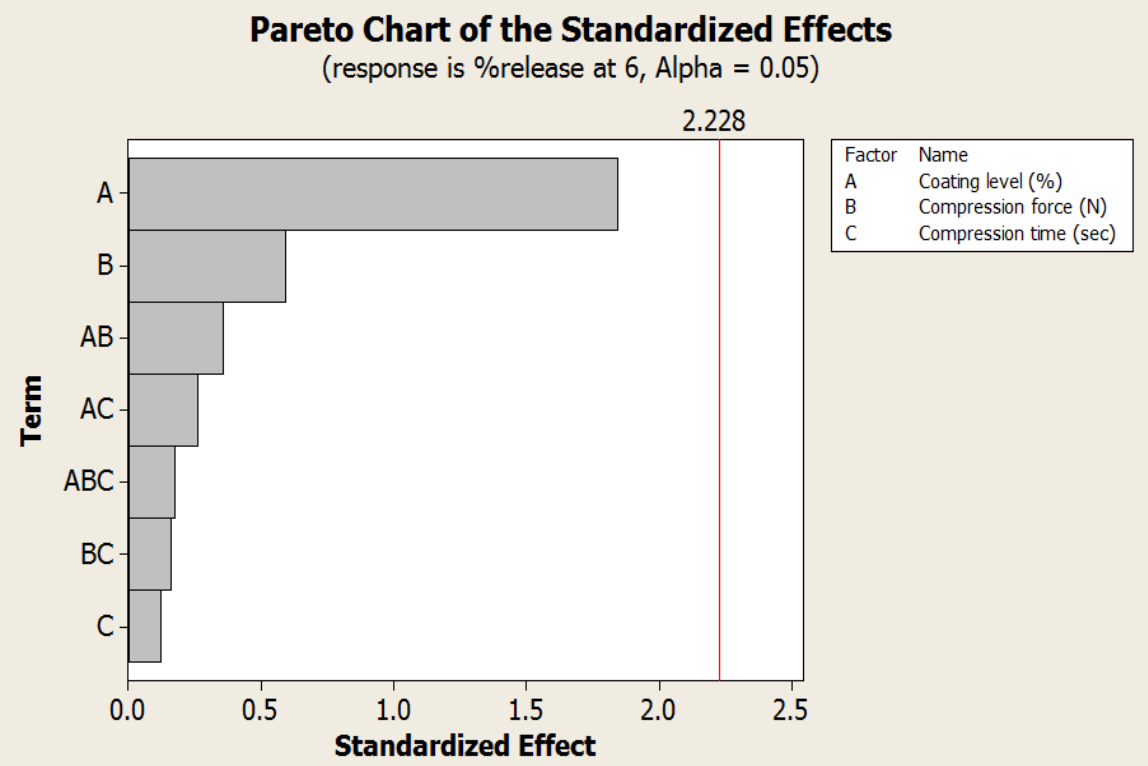

Figure 5-10: the influence of the coating level, compression force and compression time on the percentage release at 6 hrs

5.3.5 Plots of error in the model

In order to validate the design it is important to ensure that it has a normal distribution, equal variance and equal reproducibility.. The reason of applying the three assumptions is to trust the optimization in the next section of this research work.

First, the normal distribution, the used design suggested number of inputs and predicted the output as only a mean of % release, the date around the mean should have the shape of normal distribution. Figure 5-11 demonstrates the residual plots primarily to check the three assumptions about the error made by the response surface design. (at the top left) shows normal probability; it is clear that the data follow the normal distribution as all

the data are very close to the ideal distribution line. As a result of that, it is obvious that the model is fulfilling the first assumption. As shown in figure 5-11 (at the left bottom) the histogram is neglected because the histogram is sensitive to the number of experiments while the normal probability plot is not. At least 30 experiments need to be done in order to use the histogram as a tool to measure the normal distribution. For this reason it is better idea to use the normal probability plot to assess the normal distribution

Second, the equal variance or reproducibility, this assumption is to ensure the limit of error in the output when the inputs held. If the inputs are held constant, the output should have the same standard deviation. As demonstrated in figure 5-11 (at the top right), in this figure the X axis is the fitted value which represents the predicted value for % release and Y axis is the residual. Regardless to the predicting output, we should have the same error. In this figure it is obvious that all the residuals are between +5 and -5 and roughly the same spread. It is obvious that there is an equal variance of the error. The points at the top of the line are equal to the points below the line across the predicted values.

Third, the random over time assumption, Figure 5-11 (at the bottom right), shows the versus order graph, where X axis is the observation order which represents the run order, and y axis is the residual or the error between what is predicted by the model and what is observed in the lab. The reason for doing the observation order is to check the randomness of error over the time. If the random distribution was not obvious in the graph that would mean

there is another important factor that was not included in the analysis. In another words, this experiment was done to check that the order in which conducted the experiments did not introduce a bias into the design. For example, each dissolution experiment took 6 hours, and the ambient temperature was not controlled, as it might increased or decreased during the experiment, so this experiment was done to check there is no affect on the output by the ambient temperature over time. In this graph it shows that the versus order looks random over the time, and that is a prove that there was no bias effect on the output over the time

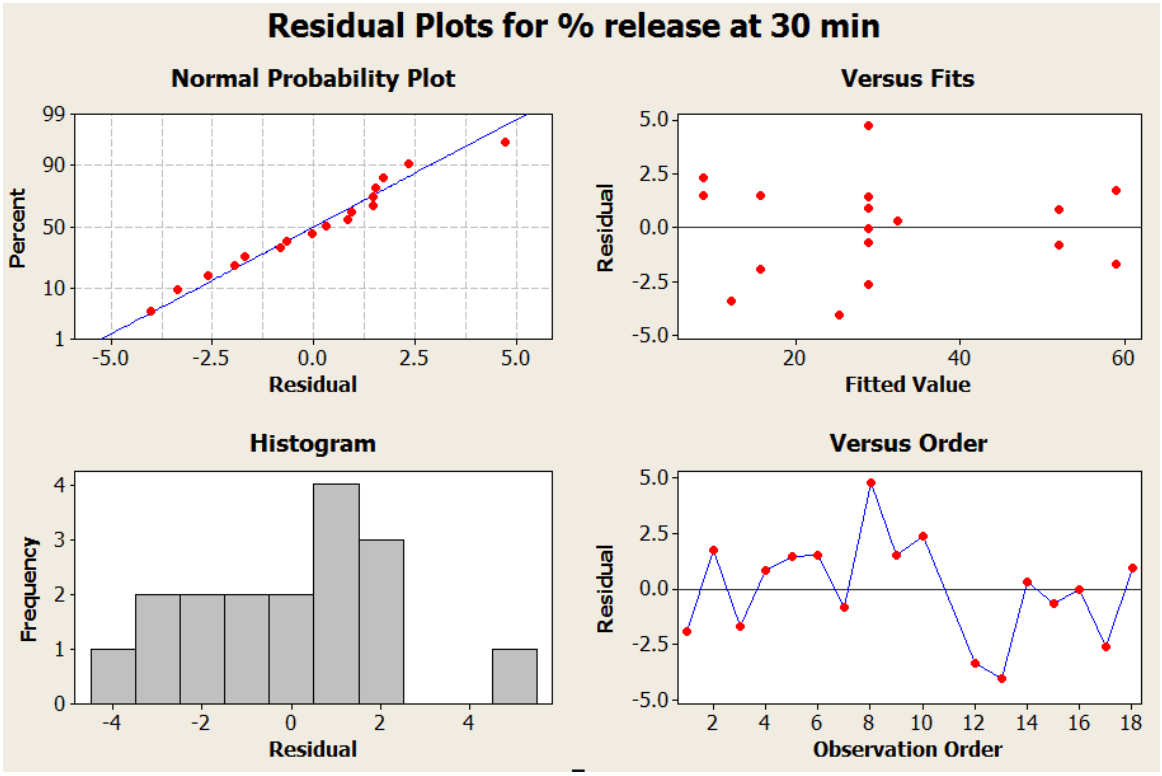

Figure 5-11: Residual Plots for percentage release at 30 min

Figure 5-12 Contour plot, it represents the effect of the inputs on the output in different way. it uses coating level percentage (X axis) against compression force (Y axis) and the response (in different levels of green colour) is the percentage release at 30 min of dissolution time. From this plot it is obvious that coating level has markedly affected the output. At high coating level the percentage of drug released was minimal and vice versa. This proves what was shown in the SEM images of compressed coated pellets at section 5.3.3, more cracks were observed when the coating level was 2.5% loading and that decreases with increasing coating level. Furthermore, the counter plot illustrated that the compression force (in the tested range), is not a significant factor as the plot show small affect of the compression force on the response (percentage release)

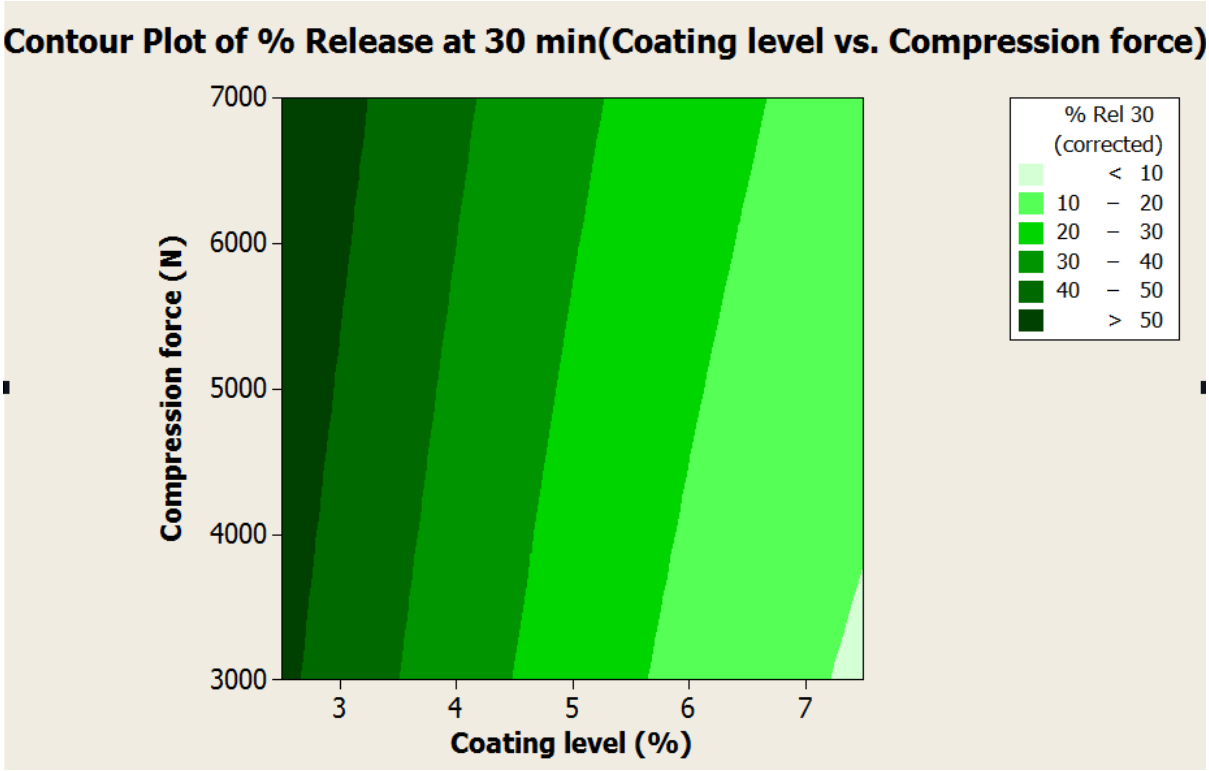

Figure 5-12: Contour plot of percentage release at 30 min coating level against compression force

Figure 5-13, illustrates the residual plot of percentage release at 6 hrs. The normal distribution fit on the design as all the points are very close to the normal distribution line. Further, the equal variance of error was obvious. It was obvious that the design has normal distribution. All of these residual plots confirm the model fits the three assumptions.

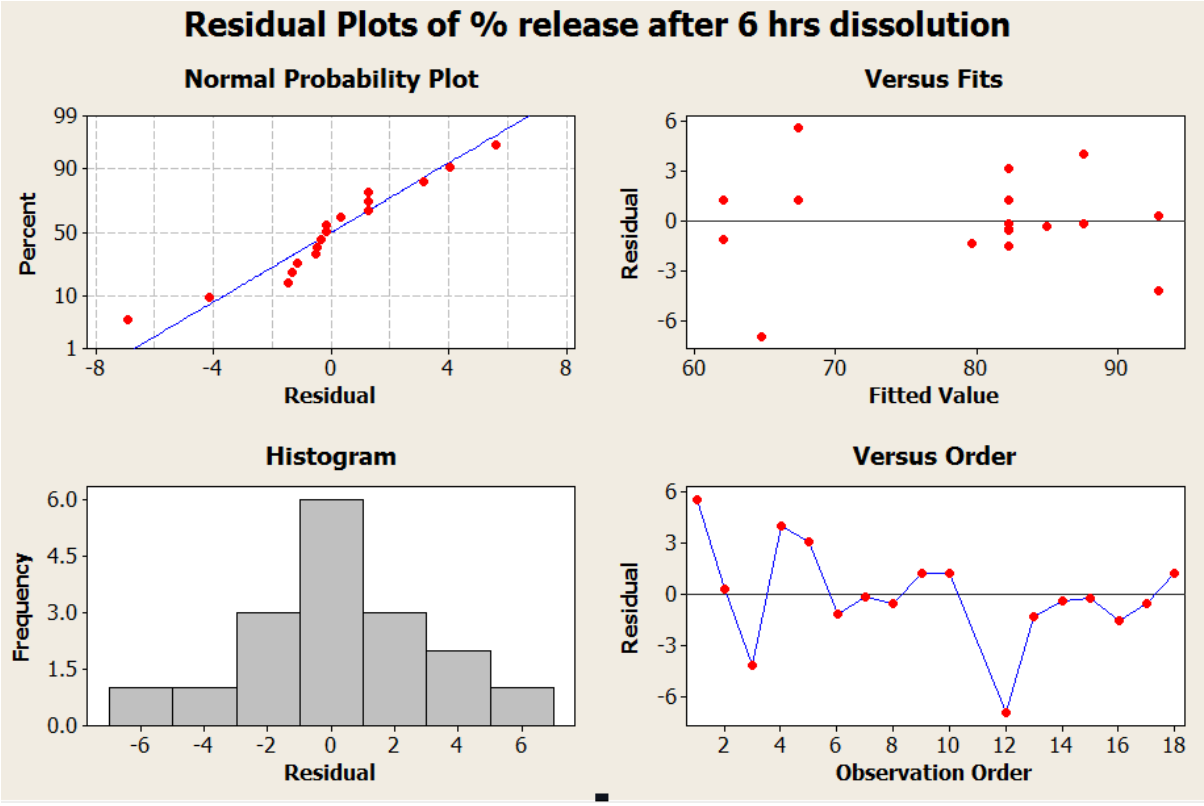

Figure 5-13: Residual plots of % release at 6 hrs dissolution

5.3.6 Optimisation of the Response surface design

Minitab16 for statistical analysis basically uses the model to find the setting of input which can give the optimum output. The design was fed with all the data including the minimum and maximum target of release as shown in figure 5-14a.

Figure 5-14b shows the obtained results when the coating level and compression force were used as input data and % Release at 30 min and at 6 hours were used as output. The desirability (D) it is a measure how well the results based on the lower and higher target, for example the lower target was 10 and higher target was 30 at 30 min dissolution awhile it was 70 lower target and 100 higher target at 6 hrs dissolution (shown in figure 5-14a). The D range from 0 to 1, in the desirability the value zero means the experiment has not reached even alpha limit, while the desirability of 1 means it hits the target perfectly. The desirability value at 30 min dissolution was 0.298 and 0.301 at 6 hours dissolution. It was found that 5.5% coating level is the optimal coating and 4778 N as the optimal compression force for minimum percentage release at 30 min and 6 hrs

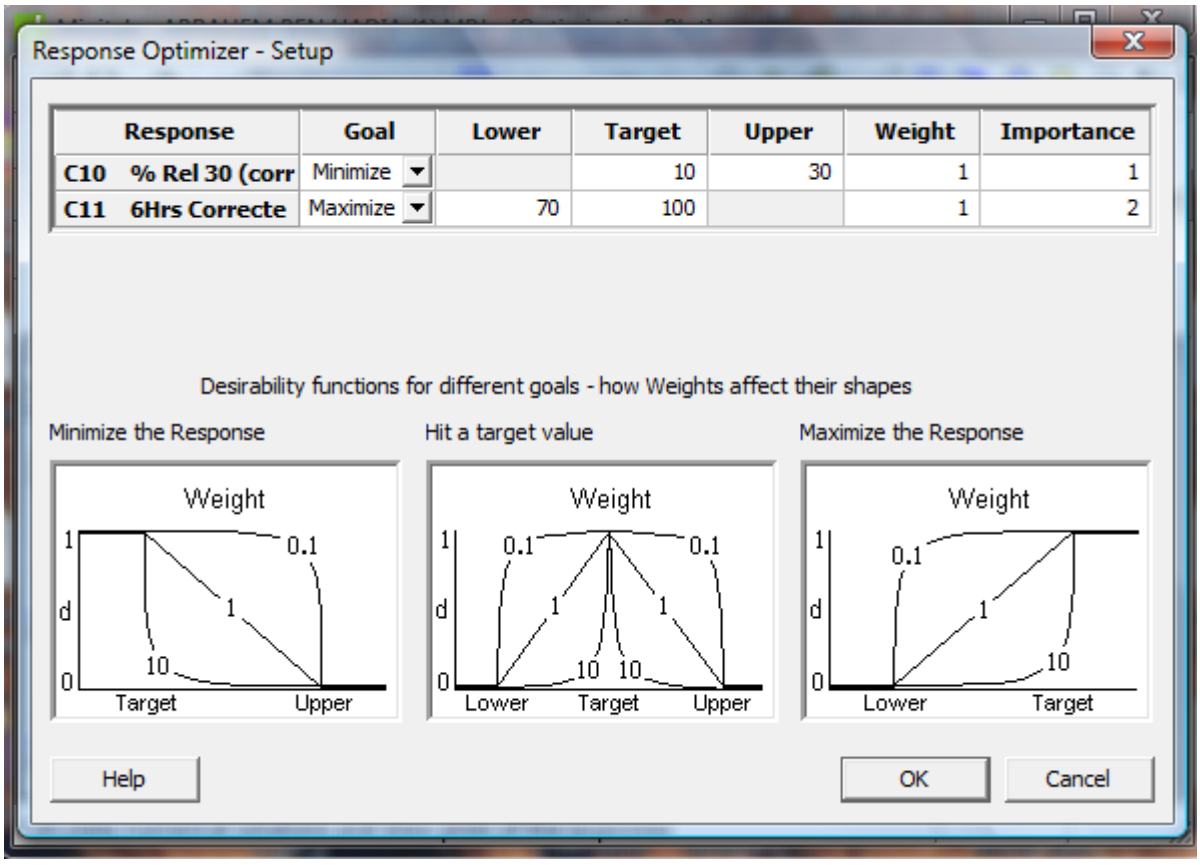

Figure 5-14a: the set up of the Response optimiser

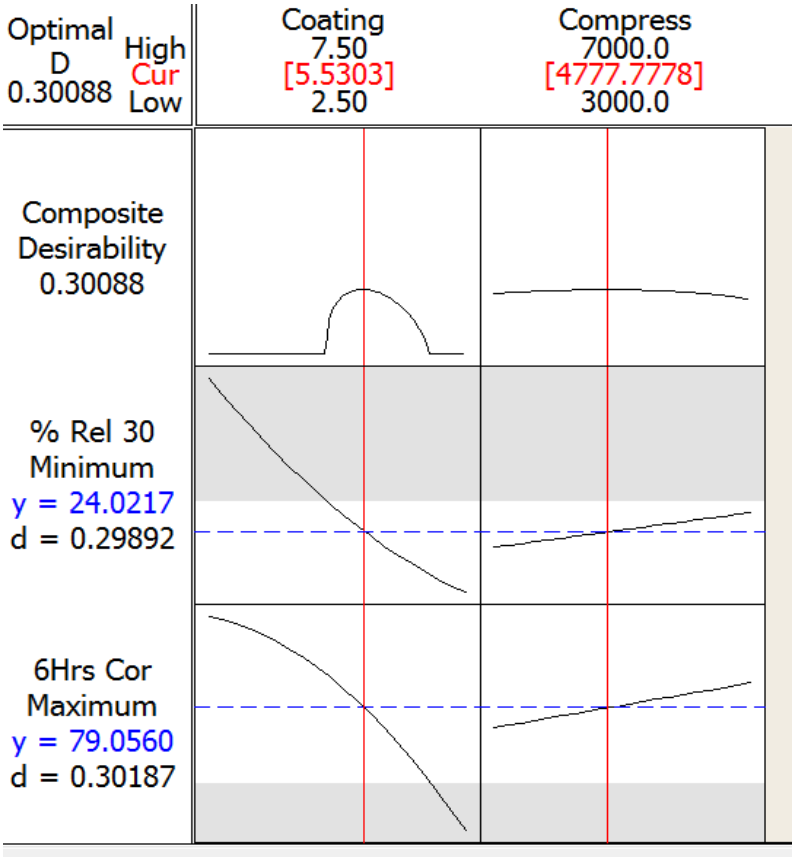

Figure 5-14b: Optimization plot of coating level and compression force at 30 min and 6hrs dissolution

5.4 Conclusion

Among the three tested parameters it was demonstrated that dwell time had no significant effect on the drug release within the range selected in this study. This could be due to the predominant elastic behaviour of ethylcellulose. Coating level was found to have the most significant effect. Compression force effect was found to be small and statistically insignificant. The model predicted that a coating level of 5.5% will produce the most desirable release profile after 30 min and 6 hours. A compression force of 4778 N was found to be the optimal value as well. SEM images showed similar results with minimal visual cracks on the 5% coating level. The interaction between these variable were studied and none of them was significant within the range applied in this study (Figures 5-8 and 5-9)

In general, it was found that a thicker coating film around the pellets improves the durability of the coating film to resist the rupture that may occur during compression process, than the thinner coating. In other words, the ability of coated pellets to undergo plastic deformation without cracking increased with increasing coating level. The error distribution plots showed that the model is reliable.

Chapter 6

Conclusion and future work

Chapter 6: Conclusion and future work

6.1 Introduction

Compression of coated pellets into MUPs offers many advantages and faces many challenges. Various process and formulation parameters have been extensively studied. However, this has been usually carried out using trial and error approach. Cushioning agents are regularly used to avoid the incidence of film rupture and the loss of coat functionality.

6.3 Findings and conclusion

The properties of ethyl cellulose coating polymer and the plasticisers (TEC and PEG400) in different formulations were studied

6.3.1 Study the thermal behaviour of free films using DSC and DMA

TGA results reveal that the level of moisture in the sample of the coating films was higher in the case of PEG 400 compared to TEC. This could be due to the hydrophilic nature of PEG 400. Moreover, TEC was clearly evaporating/degrading at much lower temperature than PEG.

The thermal behaviour of the films was studied using DSC and DMA. From the DSC results it was clear that the level of TEC has a significant influence on the Tg value; i.e., by increasing the level of TEC, the Tg value decreases. On the other hand, the inclusion of PEG 400 had less effect. Indeed, there was no significant changes in the Tg value when PEG400 level increased from 20 to 30% w/w. This suggests a lower miscibility between the polymer

and PEG400 compared to its miscibility with TEC leading to to film saturation and phase separation (Fadda et al, 2010).

During DSC experiments, a heat-cool-heat method was used to measure the Tg. This causes the loss of the residual moisture from the sample leading to higher Tg value (since water act as a plasticiser). Comparing the Tg results obtained by DSC and DMA, it was obvious that the Tg values obtained by DMA were slightly higher than DSC results. The two teqniques measures the Tg value using different approaches. The DSC looks at the changes in the heat capacity of the material as it is heated while the DMA rely on the changes in the mechanical responses of the elastic and viscous moduli as the chain mobility of the sample changes. Given our application of compression of coated pellets, DMA might be a more representative technique than DSC (Isreb, 2011).

6.3.2 Study the mechanical and rheological properties of film coating using DMA and Shear rheometer

The mechanical and rheological properties of the coating films were studied by using DMA and PPSR instruments. From the results obtained by PPSR, it was observed that the value of loss, storage and complex viscosity decreases by increasing the temperature. Moreover, the values of the of the loss and storage moduli were close to each other. There was a clear cross over point in which loss moduli overtake the storage counterpart but they remain close to each other. A horizontal shifting to the cross-over points was noticed when the temperature was increased or when a higher level of

plasticiser was used. Interestingly though a typical zero shear behaviour (terminal viscous behaviour) was not observed at any temperature which could explain why dwell time had no significant effect on film relaxation and the tendency to rupture upon die swelling. Instead at temperature higher the Tg value, both pure and plasticised coating films transformed from a predominantly elastic to weak gel-like (i.e., viscous and elastic moduli were close in value and the tan delta was close to the unity). Increasing the level of plasticizer from 0% to 30% has not influenced the elastic-viscous balance and therefore a zero-shear-viscosity plateau was not observed. The graphs of complex viscosity fit power law model which is similar to the behaviour observed with other cellulose derivative polymers (Isreb, 2011).

Meanwhile DMA analysis revealed that, as expected, the sample has a very high complex viscosity below its Tg. The elastic component was dominant in most of the samples as the values of tan delta was significantly below 1. This is expected of glassy samples below their Tg. Furthermore, during the films analysis it was found that by increasing the frequency, the tan delta decreases due to the shear thinning of thermoplastic polymers (Mezger, 2006). The shear thinning of the non-plasticised and plasticised film was clearer below the Tg value than above it which means films are more shear sensitive below the Tg than above it which is similar to what was found with other cellulose-derived polymers (Isreb, 2011) (Paradkar et al, 2008).

The value of complex viscosity obtained from both DMA and PPSR exhibits a power-law shape. The rheological moduli were affected by the type and level

of plasticiser. In other words, the more plasticiser level, the lower the moduli values. The results obtained from DMA and PPSR for complex viscosity at the same temperatures followed the same trend but they were not equal in value.

Overall the elastic nature of the samples would significantly affect the performance of the coated pellets after compression. Any stress building up in the film during the compression is likely to be stored as an internal stress and not be dissipated due to the limited chain movement and the elasticity of the film. This could results in film cracking or changes in tablet hardness over the shelf life of the product. A full relaxation zero shear viscosity was not obtainable within typical compression forces and temperatures as indicated by the DMA and shear rheometer data.

6.3.3. Study the Pellets Coating, and release profile of the coated-compressed pellets

In this research ethyl cellulose was used as a coating polymer. The selection of coating formulation was according to the thermal, mechanical and rheological studies. In this study no additive was added as cushioning agents as the project aimed at understanding the behaviour of the film under compression. Cushioning agents bulk up the tablet and reduce the overall drug load so reducing or eliminating is desirable if no adverse effect on the release profile can be achieved.

The morphology of the tabletted coated pellets was investigated using SEM. The images of the SEM show cracks on the coating film. Furthermore, it was obvious that increasing the coating level or thickness diminishes the number

of cracks although it was not avoidable. In this study 2.5, 5 and 7.5% w/w of coating level was applied on the surface of the pellets and then compacted under different compression force (3000, 5000, and 7000 N) and dwell time (0.1, 0.55 and 1 sec). The dissolution studies illustrated that coating level has the most significant effect on the percentage of release. It was found that by increasing the coating level, the percentage of release decreases. Contrary to the literature, the influence of the compression force was less significant and the dwell time showed no significant effect within the tested range. This could be due to a combination of the high elasticity of the ethylcellulose film which meant it has cracked at all the compression forces within the studied range and because the machine does not allow for longer dwell time to be tested. The DMA viscoelasticity study seems to support this finding as ethylcellulose is predominantly elastic and has a very high viscosity at ambient condition. A polymer with a more predominant loss modulus or one which is heavily plasticized would behave differently. In our study a coating level of up to 30% w/w of Tec or PEG 400 didn't seem to alter the predominant elastic behaviour of ethylcellulose significantly. It has reduced the overall viscosity though. This highlights the importance of the viscoelastic behaviour of the film at room temperature in determining the nehaviour and the selection of the key process parameters. The interactions between the three selected parameters in this study were not significant. Increasing the thickness leads to an increase in the overall strength of the film making it more resistant to cracks due to the building up of internal stresses during compression. Meanwhile the dwelling time range investigated was not likely to help the film dissipate the stress given the overall elasticity of the film (as

noted in the DMA measurements). In fact the shear rheometer data suggests no prospect of relaxation even at a higher temperature

6.4 Future work

It was found that there are more issues that can be taken further and to be studied. The relationship between complex viscosity measured by both DMA and PPSR could be further investigated. It is generally accepted that tensile moduli are 3 times higher than their shear counterpart (Mezger, 2006). In this study however we could not find a clear link between both. Fresh samples measured at the boundary temperatures could provide a more precise quantitative comparison and this allow to build a full picture about the behaviour of the films over all temperature ranges.

A comparison between complex viscosity measured using dual cantilever and tensile clamps in the DMA would be interesting. It has been previously found that complex viscosity measured using dual cantilever is more or less equal to that measured by PPSR (Isreb, 2011) when HPMCAS polymer was studied. Therefore a comparison between those two clamps of the DMA would help confirm the relationship between DMA and PPSR. Unlike dual cantilever, the tensile clamp operates with a defied shear regime which is advantageous in terms of theoretical calculations. However the expansion of the sample as temperature increases impact the precision of applying the required stress in an extensional mode.

Secondly, this study has only investigated the behaviour of ethylcellulose under compression. If more time was available, a comparison between films

plasticised with TEC and PEG 400 would be interesting. Since PEG 400 is more elastic that TEC, it would be useful to compare films of similar viscosity values, at different plasticizing levels of both TEC and PEG, in order to see if they produce comparable level of cracks and release data. Additional work is also required to expand on the factors affecting the release from the compressed pellets. A wider range of compression forces and dwell time would shed more light on their effect. In this study we were not able to examine a wider range due to the limitation of our compact simulator. A comparison between polymers with varying levels of viscoelasticity would be also interesting. It might reveal a different key process parameters than the case with EC.

Finally the relationship between rheological moduli and the percentage of release could be assessed. This requires a comparison between various formulations in terms of their rheological behaviour under various shear stresses and frequencies and the release after compression. Ultimately this research is the first step towards investigating the feasibility of using rheological measurements to inform the selection of the coating formulation as well as the compression parameters in order to achieve the required release pattern. This quality by design approach is still lagging in the field of compressed coated pellets and therefore such investigation is an essential step to enhance our understanding in this field. Achieving this knowledge would allow the reduction or the elimination of cushioning agents which will reduce the bulk of the coated pellets making them a viable alternative to tablets.

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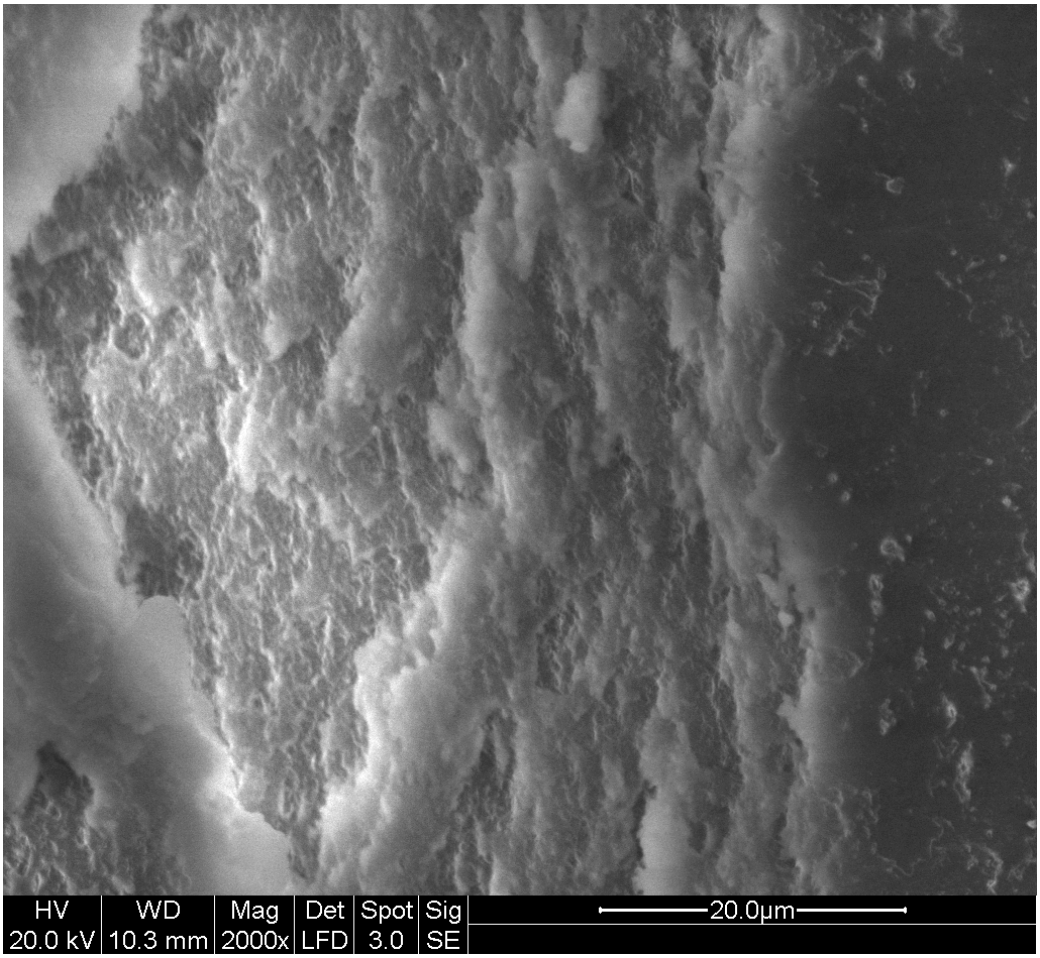
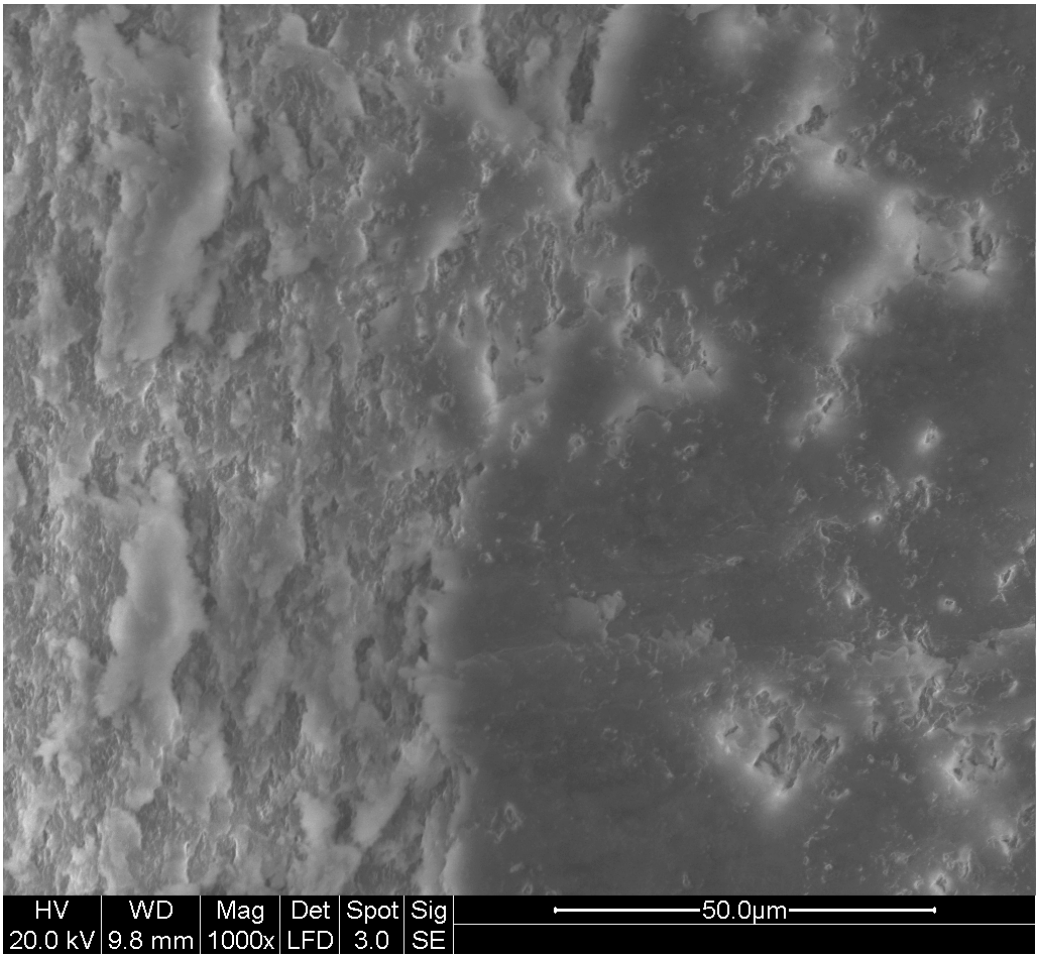
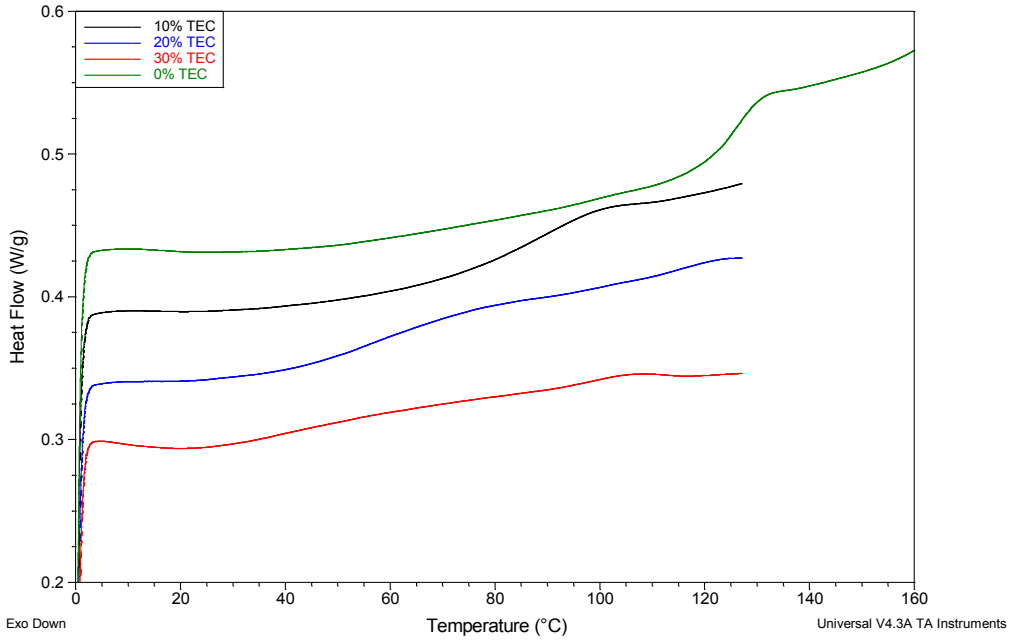
8 Appendix



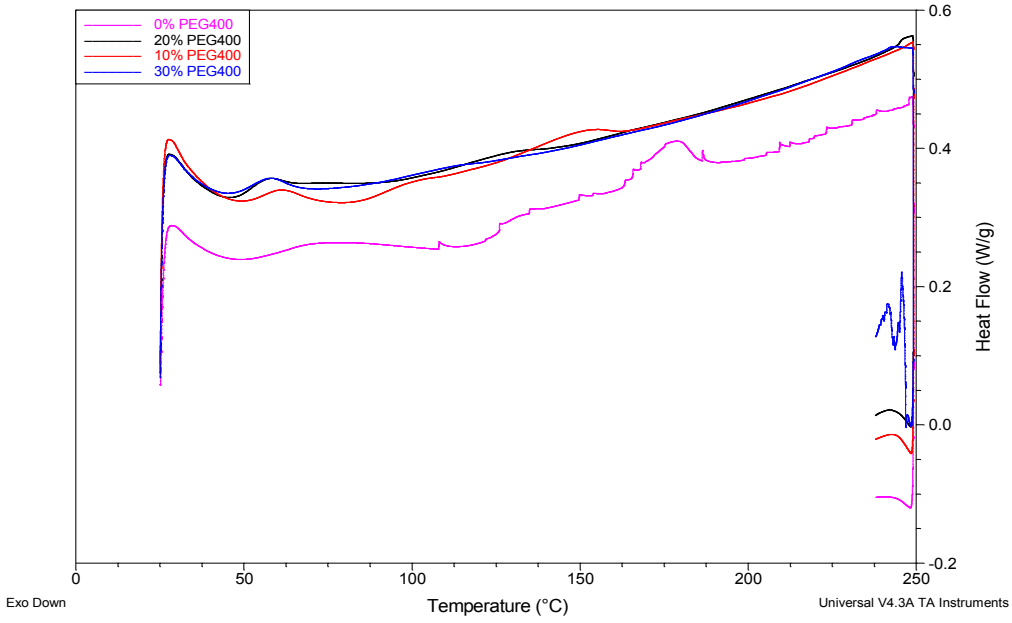
SEM image of ethyl cellulose with 10% PEG400



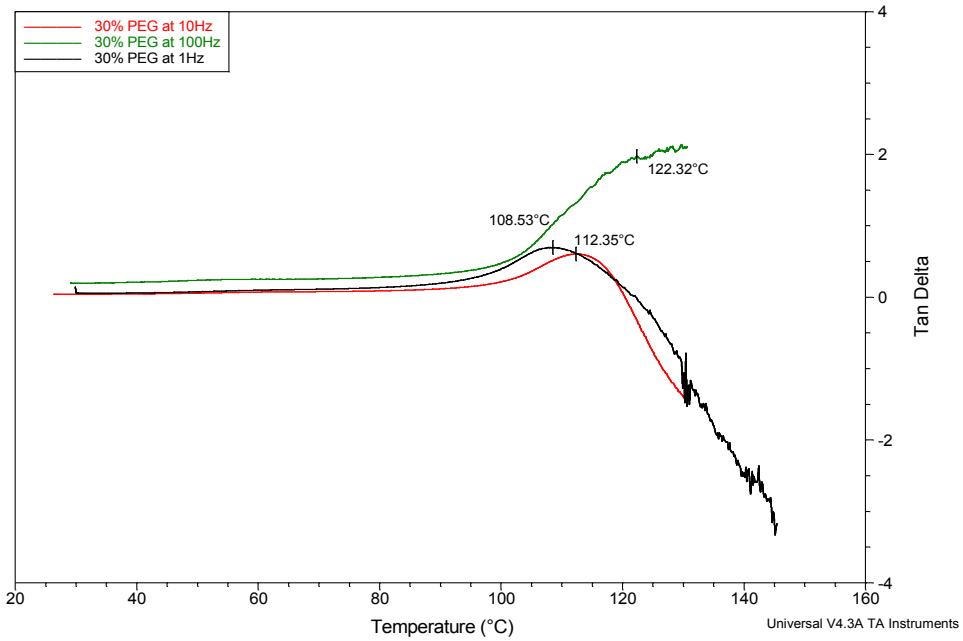
SEM image of ethyl cellulose with 20% PEG400



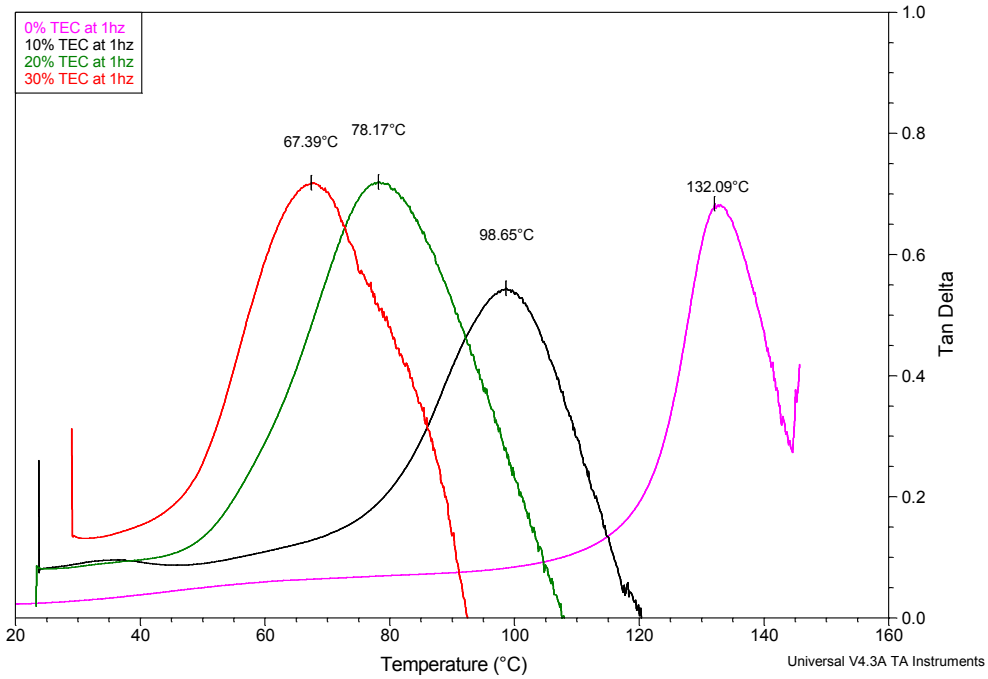
DSC thermogram of the second heating cycle of free film of ethylcellulose plasticised with 0, 10, 20, and 30% TEC



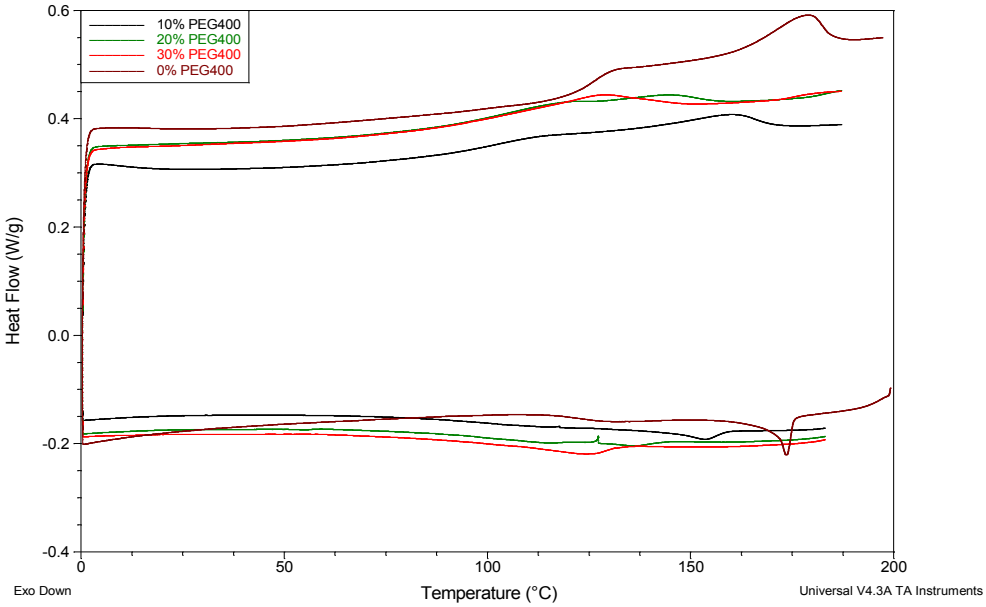
DSC study of ethylcellulose film with 0, 10, 20, and 30% PEG400



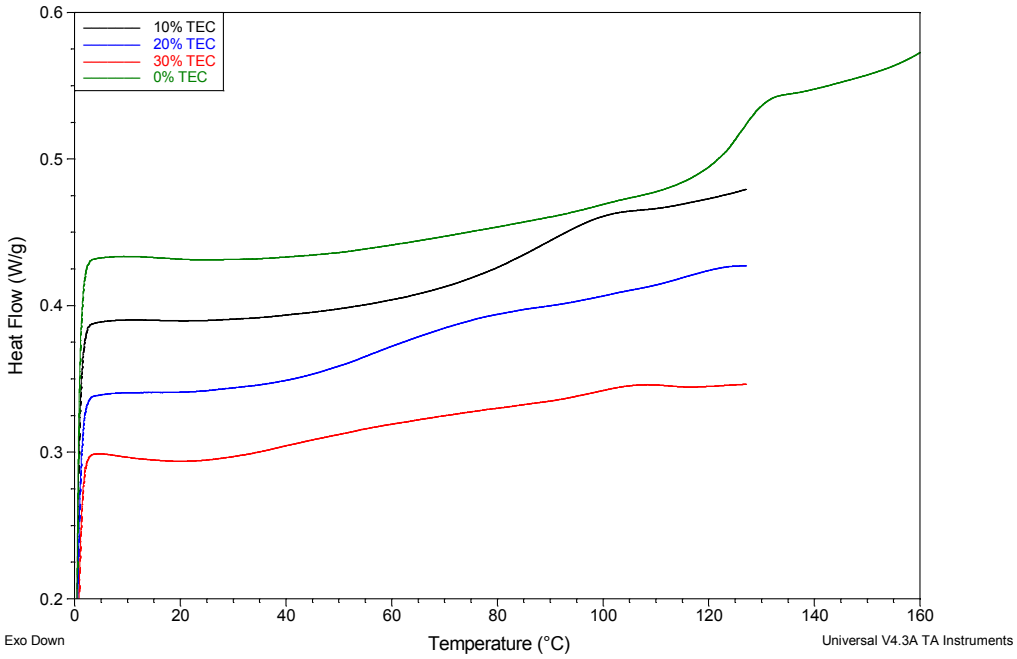
Plot of tan delta with temperature at frequencies 1, 10 and 100 Hz for films with 30% PEG400



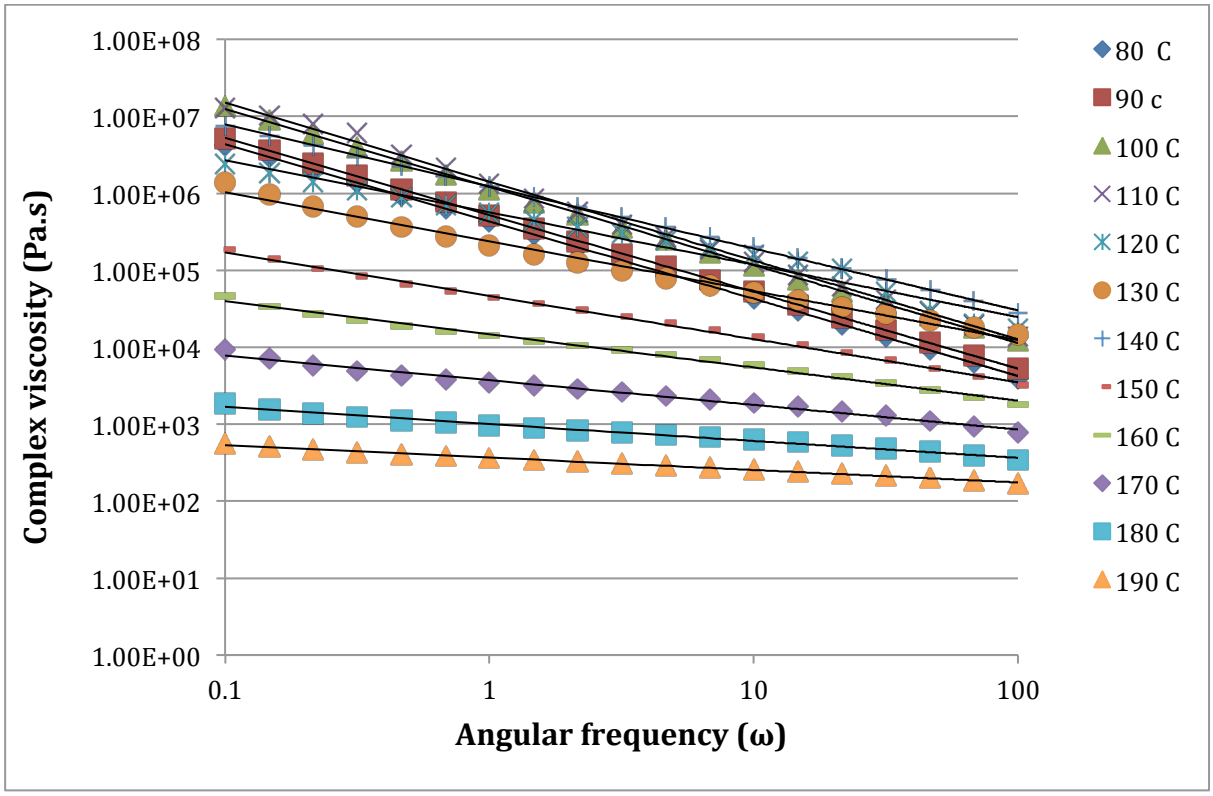
Glass transition temperatures of ethyl cellulose films with different levels of TEC measured from tan delta of the DMA



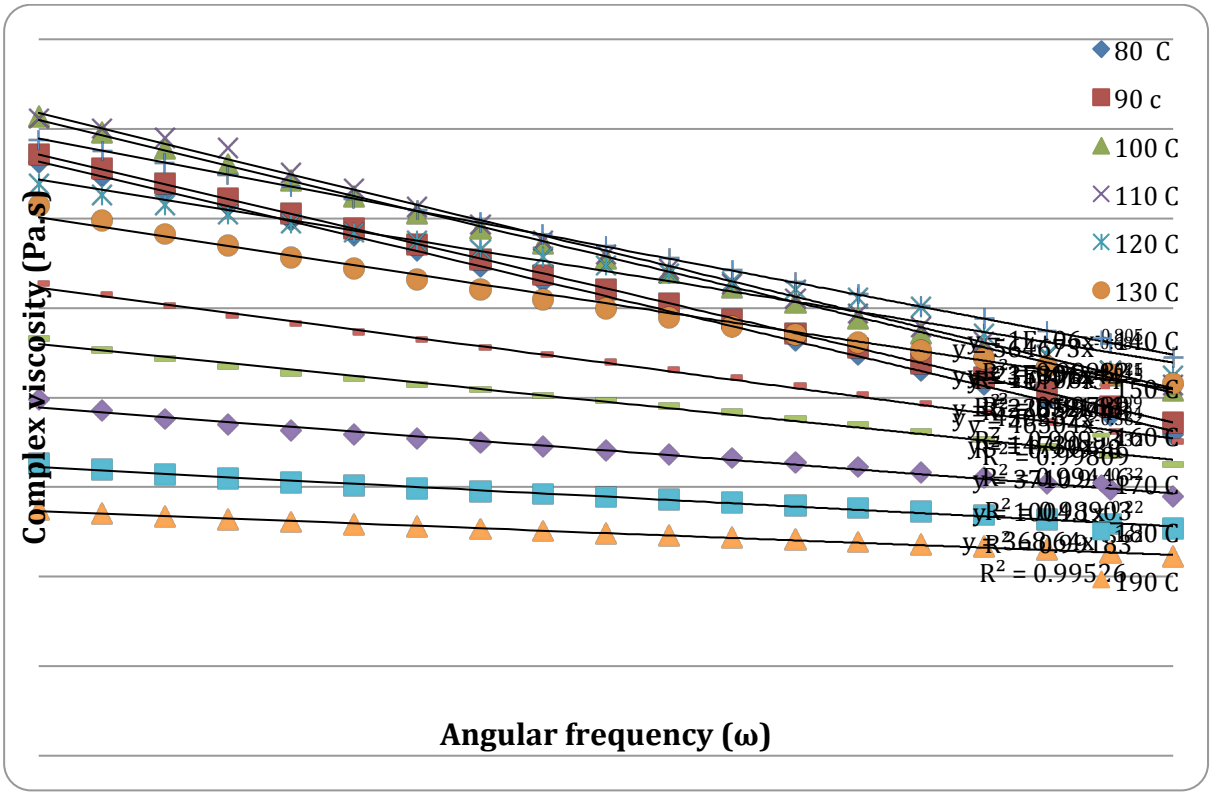
Plot of the first cycle of DSC (heat-cool-heat) of ethylcellulose film with 0, 10, 20 and 30% PEG400



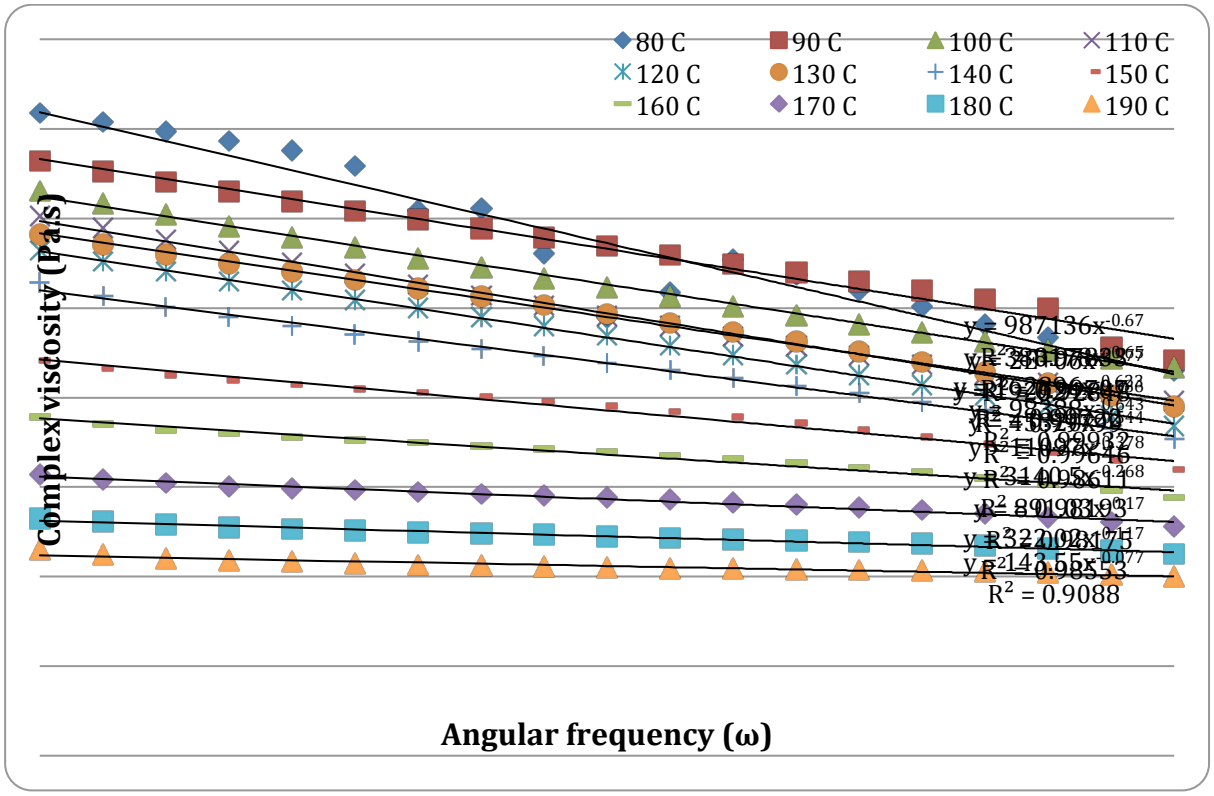
Plot of the second cycle of DSC (heat-cool-heat) of ethylcellulose film with 0, 10, 20 and 30% PEG400



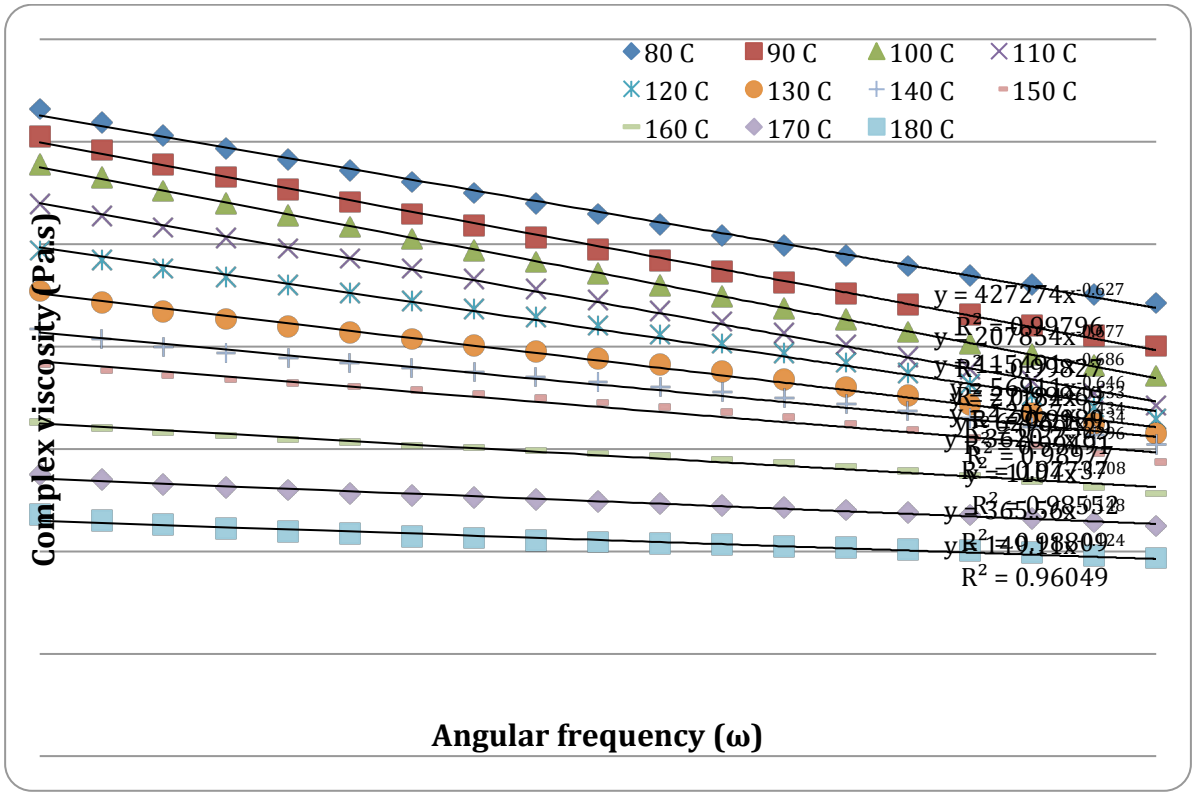
Plot of PPSH for Complex viscosity against angular frequency of pure ethyl cellulose cast film at 80 to 180 °C



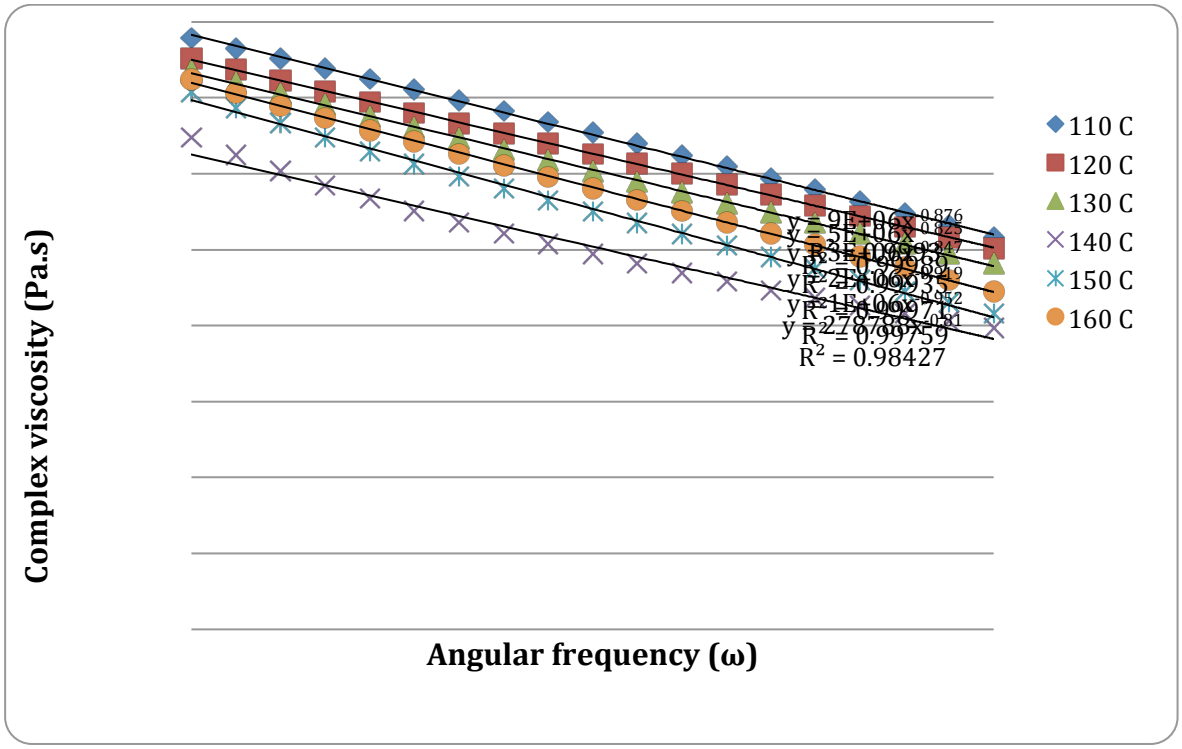
Plot of PPSH for Complex viscosity against angular frequency of ethyl cellulose film plasticized with 10% TEC at 80 to 190 °C



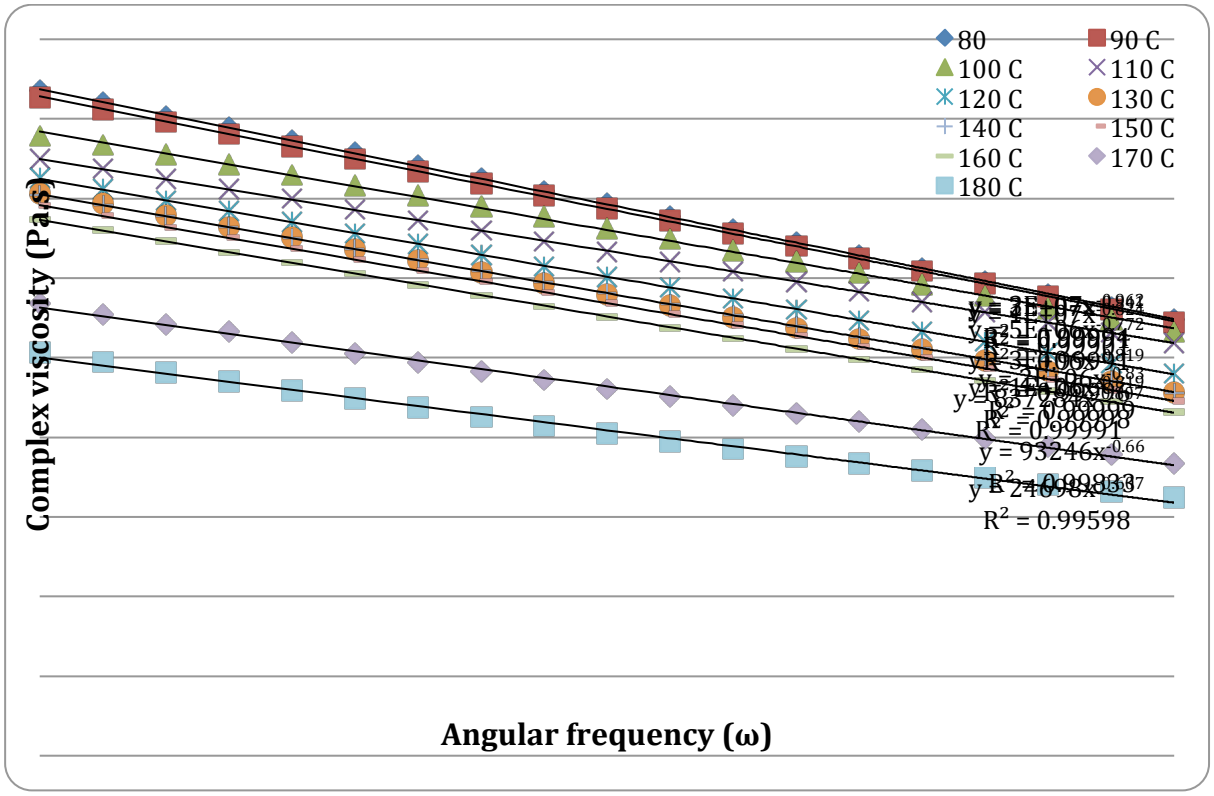
Plot of PPSH for Complex viscosity against angular frequency of ethyl cellulose film plasticized with 20% TEC at 80 to 190 °C



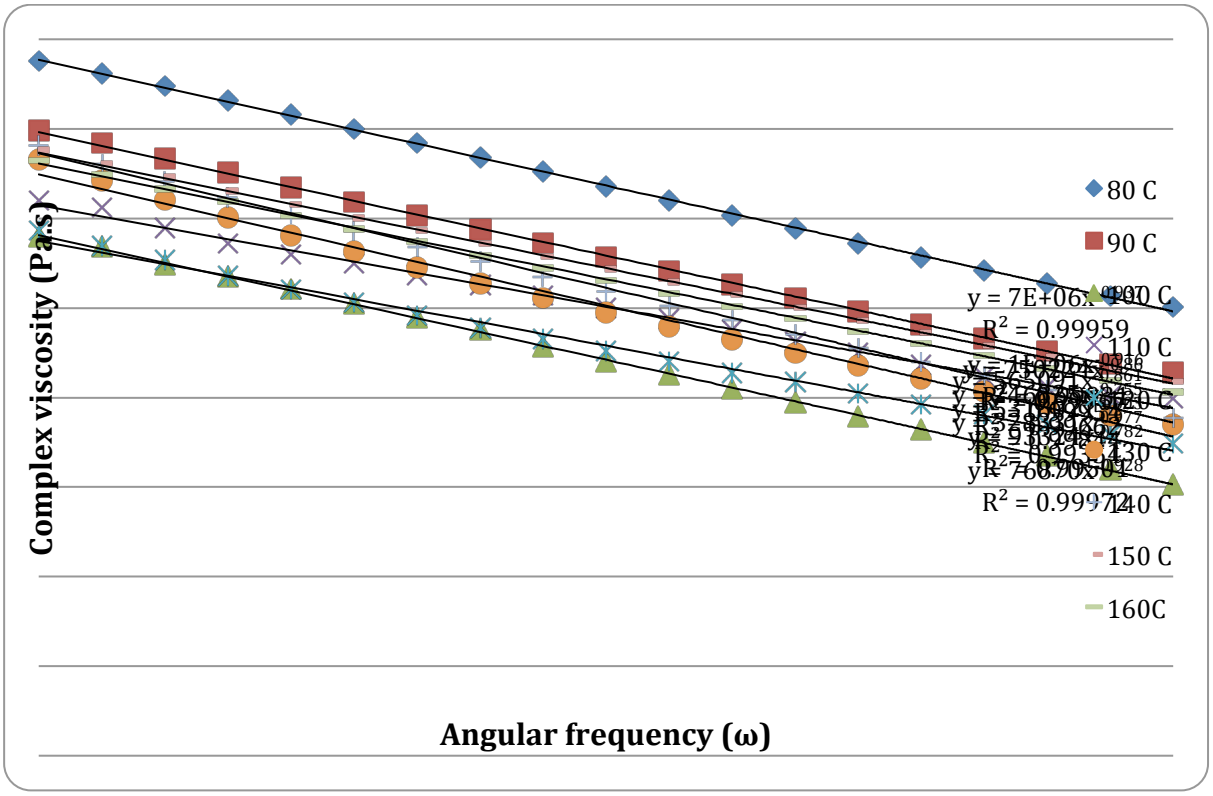
Plot of PPSH for Complex viscosity against angular frequency of ethyl cellulose film plasticized with 10% TEC at 80 to 190 °C



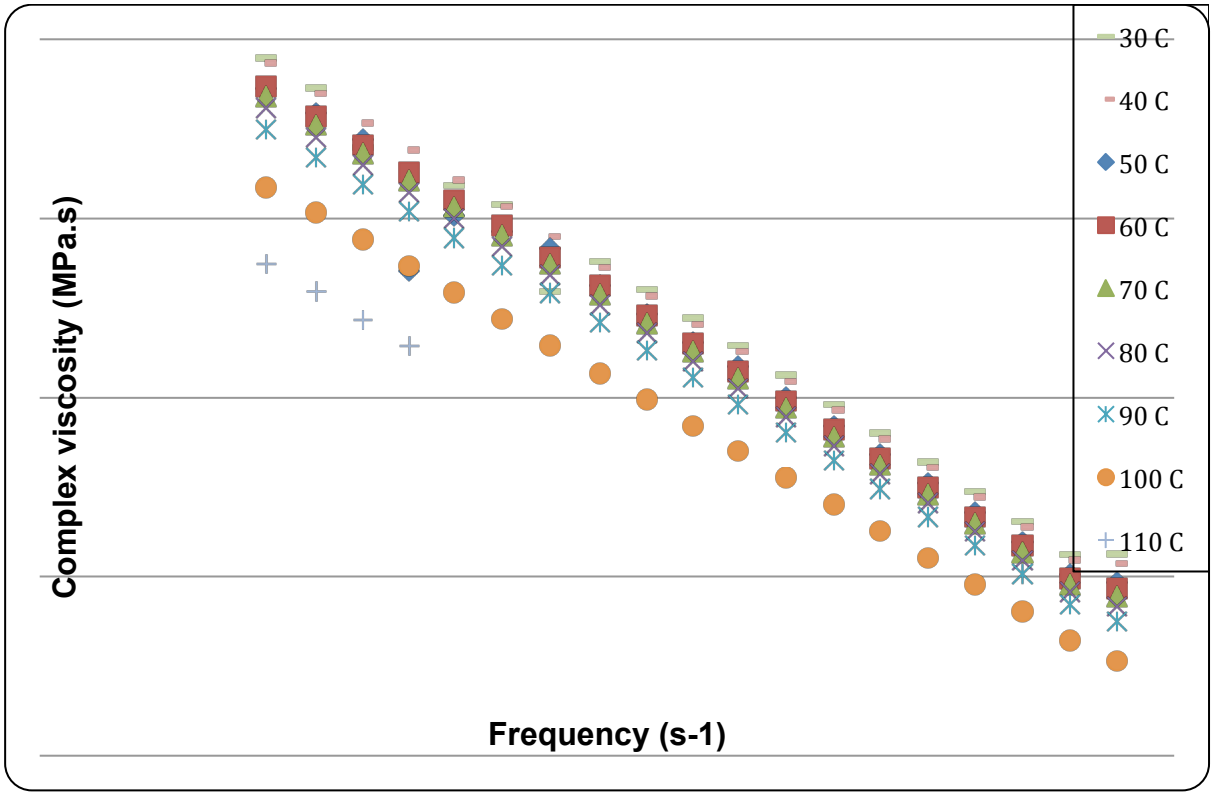
Plot of PPSH for Complex viscosity against angular frequency of ethyl cellulose film plasticized with 10% PEG400 at 110 to 160 °C



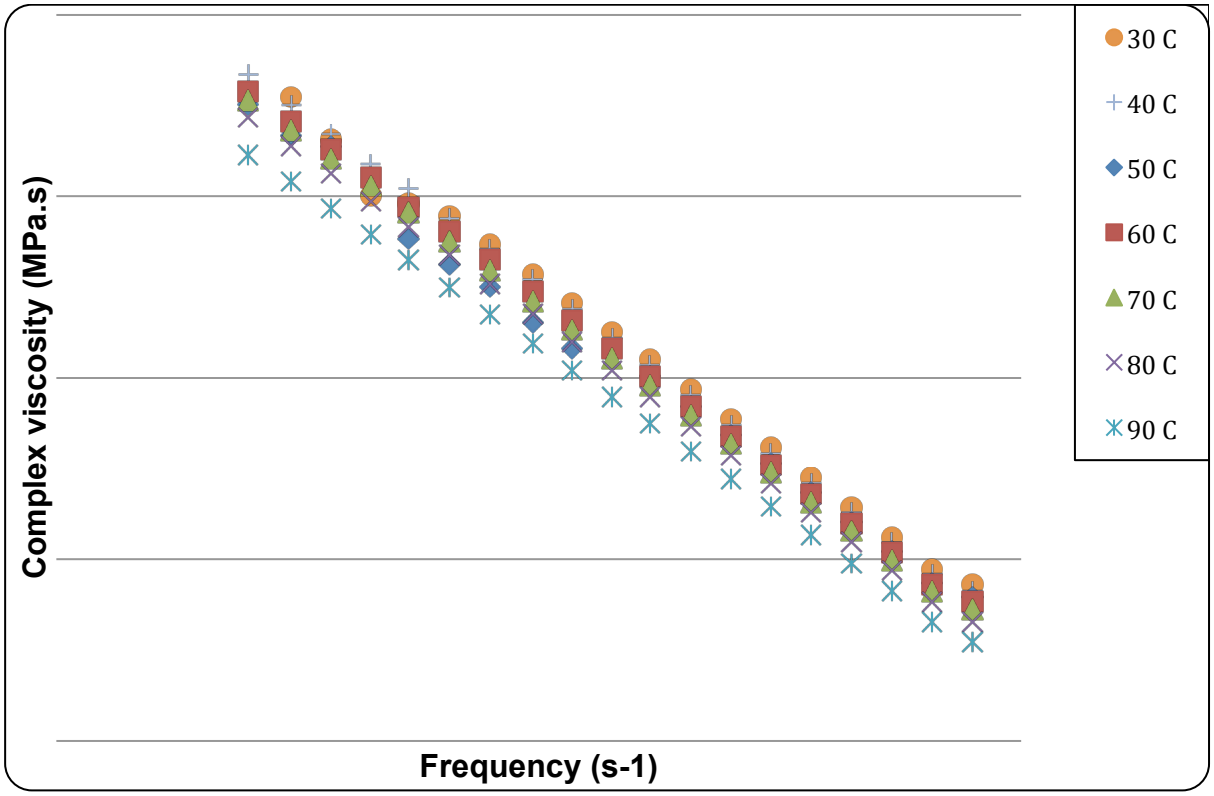
Plot of PPSH for Complex viscosity against angular frequency of ethyl cellulose film plasticized with 20% PEG400 at 80 to 180 °C



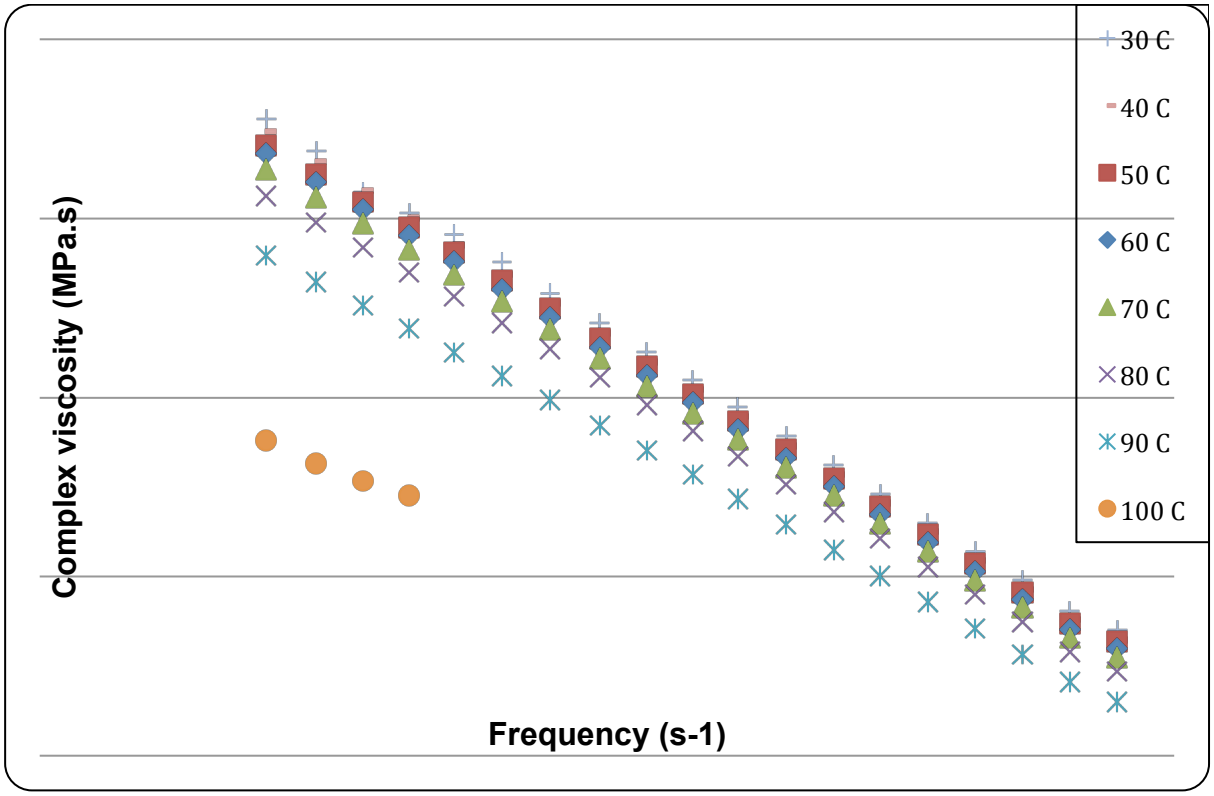
Plot of PPSH for Complex viscosity against angular frequency of ethyl cellulose film plasticized with 30% PEG400 at 80 to 160 °C



Plot of DMA for Complex viscosity against frequency of ethyl cellulose cast film plasticized with 10%PEG400 at 30 to 110 °C



Plot of DMA for Complex viscosity against frequency of ethyl cellulose cast film plasticized with 20% PEG400 at 30 to 90 °C



Plot of DMA for Complex viscosity against frequency of ethyl cellulose film plasticized with 30% PEG400 at 30 to 100 °C

DMA results of ethyl cellulose film plasticised with 30% w/w of TEC.

Time	Temp.	Frequency	Storage Modulus	Loss Modulus	Tan Delta	Complex Viscosity
min	°C	Hz	MPa	MPa		MPa·sec
5.3	30.03	0.1	811.7	27.79	0.03424	448.8
6.13	30.03	0.15	853.4	56.31	0.06599	315.1
7.95	30.01	0.22	549.7	658.4	1.198	215.5
10.52	30.01	0.32	821.6	94.75	0.1153	142.8
13.09	30.01	0.46	845.3	24.27	0.02871	101.6
15.67	30	0.68	890.3	59.29	0.06659	72.51
17	30	1	807	87.58	0.1085	44.86
17.12	30	1.5	860.5	95.38	0.1108	31.9
17.46	30	2.2	878.2	94.87	0.108	22.19
17.99	30	3.2	894.9	95.02	0.1062	15.54
18.53	30.01	4.6	907.9	96.75	0.1066	10.97
19.07	30.01	6.8	921.8	99.05	0.1074	7.535
19.38	30.01	10	936.8	101.8	0.1087	5.208
19.57	30.01	14.6	950.4	105.3	0.1108	3.619
19.78	30.01	21.5	965.8	109.5	0.1134	2.498
19.99	30.01	31.6	979.9	114.9	0.1172	1.725
20.28	30.01	46.4	992	130.9	0.132	1.192
20.47	30	68	1000	121.7	0.1217	0.819
20.56	30	100	1101	147.4	0.1338	0.6141
29.45	40.02	0.1	676.4	72.41	0.1071	375.9
30.24	40.01	0.15	683.1	73.08	0.107	253.1
32.03	40.01	0.22	688.7	74.32	0.1079	174
34.58	40.01	0.32	763.2	57.44	0.07526	132.2
37.15	40	0.46	739.1	85.14	0.1152	89.38
39.72	40	0.68	740.6	66.52	0.08982	60.43
41.05	40	1	732.8	74.84	0.1021	40.71
41.16	40	1.5	742.8	77.31	0.1041	27.51
41.5	40	2.2	751.4	79.94	0.1064	18.98
42.04	40	3.2	762.4	81.85	0.1074	13.24
42.59	40	4.6	774.2	83.92	0.1084	9.356
43.13	40	6.8	787.6	86.33	0.1096	6.439
43.44	40	10	802.9	88.83	0.1106	4.464
43.63	40	14.6	816.3	92.36	0.1131	3.11
43.85	40	21.5	831.7	96.02	0.1154	2.152
44.06	40	31.6	845.6	100.9	0.1193	1.489
44.35	40	46.4	862.3	111.6	0.1294	1.036
44.55	40	68	866	106.6	0.1231	0.7091
44.64	40	100	924.5	128.9	0.1394	0.5158
5.3	50.01	0.1	52.32	81.92	1.566	53.72
6.13	50.1	0.15	94.46	11.08	0.1173	35.04

7.94	50.11	0.22	106.9	38.79	0.3628	28.57
10.5	49.99	0.32	37.21	37.3	1.003	9.099
13.07	50	0.46	55.94	18.46	0.3299	7.076
15.64	50	0.68	85.59	46.88	0.5478	7.931
16.99	50	1	42.31	25.19	0.5954	2.721
17.14	50	1.5	112.3	37.18	0.3311	4.357
17.51	50	2.2	71.83	139.5	1.942	3.941
18.08	50	3.2	153.6	52.08	0.3391	2.801
18.65	50	4.6	184.5	59.83	0.3244	2.33
19.23	50	6.8	201.1	57.79	0.2874	1.7
19.56	50	10	215.4	62.95	0.2923	1.24
19.75	50	14.6	230.2	66.85	0.2904	0.9074
19.97	50	21.5	247	70.64	0.286	0.6602
20.18	50	31.6	264.3	74.73	0.2828	0.4803
20.47	50	46.4	283.7	83.52	0.2944	0.3522
20.66	50	68	297	80.01	0.2694	0.25
20.75	50	100	333.3	103.7	0.3112	0.1929
29.82	60.03	0.1	15.07	10.4	0.69	10.12
30.61	60.02	0.15	17.33	11.61	0.6702	7.685
32.4	60.02	0.22	19.27	12.8	0.6641	5.812
34.95	60.02	0.32	21.73	14.4	0.6626	4.501
37.49	60	0.46	24.92	16.12	0.6469	3.565
40.03	60	0.68	28.52	17.79	0.6236	2.732
41.35	60	1	33.07	19.75	0.5972	2.129
41.46	60	1.5	38.39	22.68	0.5907	1.643
41.8	60	2.2	44.61	25.41	0.5696	1.29
42.36	60	3.2	3.744	2.966	0.7921	0.08249
42.92	60	4.6	2.149	1.204	0.5602	0.02959
43.48	60	6.8	4.565	3.167	0.6937	0.04515
43.82	60	10	9.099	4.732	0.52	0.05668
44.04	60	14.6	19.42	14.08	0.725	0.09078
44.28	60	21.5	38.95	23.72	0.609	0.1172
44.53	60	31.6	72.72	39.41	0.5419	0.1446
44.84	60	46.4	112.1	55.4	0.4943	0.1489
45.04	60	68	126.9	54.93	0.4327	0.1124
45.14	60	100	147.8	70.27	0.4755	0.09042
54.5	70.03	0.1	2.332	0.9619	0.4125	1.394
55.3	70.02	0.15	3.079	2.294	0.7449	1.414
57.09	70.02	0.22	3.87	3.004	0.7761	1.231
59.64	70.01	0.32	0.2352	0.1779	0.7565	0.05094
62.21	70.01	0.46	0.1844	0.09049	0.4909	0.02467
64.78	70.01	0.68	0.1261	0.1183	0.938	0.01405
66.12	70.01	1	0.4261	0.4372	1.026	0.03374
66.63	70.01	2.2	0.1407	0.07367	0.5237	0.003989
67.2	70.01	3.2	0.178	0.173	0.972	0.004287

67.77	70.01	4.6	0.5413	0.4807	0.8879	0.008697
68.33	70	6.8	1	0.8863	0.8862	0.01086
68.67	70	10	2.292	1.831	0.7987	0.01621
68.88	70	14.6	6.4	6.475	1.012	0.03446
69.11	70	21.5	18.8	14.69	0.7814	0.06134
69.34	70	31.6	33.45	21.95	0.6562	0.06998
69.64	70	46.4	42.53	29.91	0.7033	0.06193
69.83	70	68	47.21	27.39	0.5802	0.04435
69.93	70	100	52.88	37.42	0.7077	0.0358
79.36	80.03	0.1	1.101	0.6904	0.6273	0.718
80.16	80.03	0.15	1.198	0.823	0.687	0.5355
81.95	80.02	0.22	1.329	0.9283	0.6985	0.4072
84.5	80.01	0.32	1.465	1.05	0.7166	0.3112
87.06	80.01	0.46	1.401	1.312	0.936	0.2306
89.63	80	0.68	2.52	1.785	0.7083	0.251
90.96	80	1	3.238	1.924	0.5941	0.2082
91.09	80	1.5	3.498	2.508	0.717	0.1586
91.46	80	2.2	4.082	2.881	0.7059	0.1255
92.03	80	3.2	4.791	3.489	0.7282	0.1024
92.6	80	4.6	5.766	4.034	0.6996	0.08453
93.17	80	6.8	6.873	4.937	0.7184	0.06877
93.49	80	10	8.247	5.835	0.7076	0.05583
93.68	80	14.6	9.853	6.969	0.7073	0.04568
93.9	80	21.5	12.06	8.278	0.6862	0.03761
94.12	80	31.6	14.43	9.876	0.6842	0.03059
94.41	80	46.4	19.12	15.48	0.8097	0.02931
94.6	80	68	19.52	11.4	0.5838	0.01837
94.69	80	100	17.29	21.73	1.257	0.01535
104.35	90.03	0.1	0.3707	0.2239	0.6042	0.2393
105.14	90.03	0.15	0.3948	0.2492	0.6312	0.172
106.93	90.02	0.22	0.4303	0.2717	0.6315	0.1278
109.47	90.01	0.32	0.4688	0.3069	0.6547	0.09676
112.03	90.01	0.46	0.18	0.1268	0.7047	0.02645
114.59	90	0.68	0.105	0.09214	0.8778	0.01135
115.93	90	1	0.2823	0.2073	0.7345	0.01935
116.06	90	1.5	0.3629	0.2637	0.7266	0.01652
116.42	90	2.2	0.3771	0.2413	0.6398	0.01124
116.98	90	3.2	0.5299	0.347	0.6549	0.01094
117.53	90	4.6	0.9011	0.6497	0.721	0.01335
118.09	90	6.8	1.678	1.161	0.6921	0.01658
118.42	90	10	2.741	1.789	0.6528	0.01809
118.61	90	14.6	4.159	2.559	0.6153	0.01848
118.83	90.01	21.5	6.011	3.518	0.5852	0.0179
119.04	90.01	31.6	7.762	4.595	0.592	0.01577
119.33	90.01	46.4	11.38	10.44	0.9175	0.0184

119.52	90.01	68	11.89	5.477	0.4606	0.01064
119.61	90.01	100	16.1	24.61	1.529	0.01625

DMA results of ethyl cellulose film plasticised with 30% w/w of PEG400

Time	Temp.	Frequency	Storage Modulus	Loss Modulus	Tan Delta	Complex Viscosity
min	°C	Hz	MPa	MPa		MPa·sec
5.3	30.03	0.1	647.4	62.96	0.09725	359.5
6.13	30.03	0.15	650.1	30.5	0.04691	239.8
7.95	30.02	0.22	519.1	197.5	0.3804	139.5
10.52	30.01	0.32	621	33.97	0.05469	107.4
13.09	30.01	0.46	659	160.8	0.244	81.49
15.67	30.01	0.68	698.9	34.58	0.04948	56.87
17	30.01	1	690	42.95	0.06225	38.2
17.12	30.01	1.5	706.6	41.49	0.05872	26.08
17.46	30.01	2.2	716.2	41.96	0.05858	18.02
17.99	30	3.2	726	42.56	0.05862	12.56
18.53	30	4.6	735.5	43.53	0.05919	8.852
19.06	30	6.8	746.2	44.82	0.06006	6.075
19.37	30	10	756.7	46.37	0.06129	4.189
19.56	30	14.6	766.9	48.4	0.06311	2.909
19.77	30	21.5	777.8	50.92	0.06547	2.003
19.98	30	31.6	788	54.15	0.06871	1.381
20.27	30	46.4	798.4	62.48	0.07825	0.9538
20.45	30	68	786.9	58.07	0.07379	0.6413
20.55	30	100	908	87.91	0.09682	0.5041
29.45	40.02	0.1	553.3	49.1	0.08875	306.9
30.24	40.01	0.15	562.3	45.73	0.08132	207.8
32.03	40.01	0.22	568.2	44.81	0.07886	143.2
34.58	40.02	0.32	579.3	42.81	0.07389	100.3
37.15	40	0.46	590.4	43.89	0.07434	71.12
39.72	40	0.68	600.3	43.36	0.07224	48.91
41.04	40	1	608.6	43.66	0.07174	33.72
41.16	40	1.5	619.1	43.89	0.0709	22.86
41.5	40	2.2	628.9	44.15	0.07019	15.84
42.04	40	3.2	639.1	44.49	0.06962	11.06
42.58	40	4.6	648.9	45.09	0.06949	7.815
43.12	40	6.8	659.7	46.04	0.06979	5.374
43.44	40	10	670.5	47.19	0.07038	3.715
43.63	40	14.6	681	48.91	0.07182	2.584
43.84	40	21.5	692.1	50.94	0.0736	1.784

44.06	40	31.6	702.6	53.65	0.07636	1.232
44.35	40	46.4	713.5	61.49	0.08618	0.8529
44.54	40	68	705.9	56.55	0.08011	0.5755
44.63	40	100	796.7	83.7	0.1051	0.4427
5.29	50.07	0.1	458.5	62.17	0.1356	255.7
6.08	50.1	0.15	473.3	58.2	0.123	175.7
7.87	50.07	0.22	490.2	56.03	0.1143	123.9
10.41	50.04	0.32	512.1	53.39	0.1043	88.92
12.95	49.99	0.46	532.9	51.34	0.09633	64.32
15.49	50	0.68	551.4	50	0.09068	45
16.8	50	1	566.5	49.12	0.08671	31.42
16.92	50	1.5	578.5	48.93	0.08457	21.39
17.26	50	2.2	590.1	48.88	0.08282	14.87
17.79	50	3.2	602.1	48.88	0.08118	10.43
18.33	50	4.6	613.8	49.1	0.08	7.397
18.87	50	6.8	626.1	49.75	0.07946	5.104
19.18	50	10	638	50.7	0.07947	3.537
19.37	50	14.6	649.2	52.17	0.08035	2.465
19.58	50	21.5	661.2	54.04	0.08173	1.705
19.79	50	31.6	672.3	56.48	0.08401	1.18
20.07	50	46.4	683.4	63.96	0.0936	0.8175
20.26	50	68	673.3	57.57	0.08551	0.5492
20.35	50	100	786.1	89.64	0.114	0.4372
29.41	60.03	0.1	414.2	58.01	0.1401	231.1
30.2	60.02	0.15	428.7	58.48	0.1364	159.4
31.98	60.02	0.22	442.5	56.12	0.1268	112
34.52	60.01	0.32	458.7	54.13	0.118	79.77
37.06	60.01	0.46	474.6	52.48	0.1106	57.36
39.6	60.01	0.68	490.6	51.15	0.1042	40.09
40.92	60	1	504.9	50.29	0.0996	28.04
41.03	60.01	1.5	517.2	50.01	0.09669	19.14
41.37	60	2.2	528.9	49.71	0.09398	13.34
41.91	60	3.2	540.8	49.63	0.09178	9.378
42.45	60	4.6	552.3	49.85	0.09026	6.663
43	60.01	6.8	564.6	50.4	0.08926	4.607
43.31	60.01	10	576.6	51.13	0.08868	3.199
43.5	60.01	14.6	588.1	52.5	0.08928	2.235
43.72	60.01	21.5	600.2	54.19	0.09029	1.549
43.93	60.01	31.6	611.5	56.39	0.09222	1.074
44.22	60.01	46.4	623.3	63.53	0.1019	0.7462
44.41	60.01	68	617.3	57.54	0.09321	0.5039
44.5	60.01	100	710.1	86.5	0.1218	0.3953
53.87	70.03	0.1	334.4	63.98	0.1913	188.1
54.66	70.02	0.15	350.3	60.13	0.1717	130.9
56.44	70.02	0.22	366.3	57.95	0.1582	93.16

58.98	70.01	0.32	383.2	56.75	0.1481	66.9
61.52	70.01	0.46	400.1	55.37	0.1384	48.53
64.06	70	0.68	417.2	53.82	0.129	34.19
65.38	70	1	432.3	53.11	0.1229	24.07
65.49	70	1.5	445.3	52.78	0.1185	16.52
65.84	70	2.2	457.7	52.34	0.1144	11.57
66.38	70	3.2	470.3	52.17	0.1109	8.172
66.92	70	4.6	482.2	52.26	0.1084	5.827
67.46	70	6.8	495.2	52.62	0.1063	4.047
67.77	70	10	507.8	53.13	0.1046	2.822
67.96	70	14.6	519.8	54.38	0.1046	1.978
68.18	70	21.5	532.4	55.75	0.1047	1.376
68.39	70	31.6	544.3	57.75	0.1061	0.9572
68.69	70	46.4	557.1	64.55	0.1159	0.6679
68.88	70	68	554.5	58.86	0.1062	0.4532
68.97	70	100	634	85.17	0.1343	0.3535
78.45	80.03	0.1	234.6	59.55	0.2539	133.7
79.24	80.02	0.15	252	59.15	0.2347	95.38
81.03	80.02	0.22	267	58.88	0.2205	68.68
83.56	80.01	0.32	283.3	58.58	0.2068	49.96
86.1	80.01	0.46	298.7	57.93	0.1939	36.55
88.65	80	0.68	316.8	56.9	0.1796	26.16
89.96	80	1	332.1	56.85	0.1712	18.62
90.08	80	1.5	346.2	57.09	0.1649	12.93
90.42	80	2.2	359.2	56.76	0.158	9.134
90.96	80	3.2	372.5	56.64	0.1521	6.507
91.51	80	4.6	385.5	56.88	0.1476	4.681
92.05	80	6.8	399.1	57.37	0.1438	3.276
92.36	80	10	412.7	57.79	0.14	2.303
92.56	80	14.6	424.9	59	0.1388	1.624
92.77	80	21.5	438.3	60.33	0.1376	1.137
92.99	80	31.6	450.6	62.25	0.1381	0.7956
93.28	80	46.4	464.1	68.84	0.1483	0.5588
93.48	80	68	463.9	63.01	0.1358	0.3805
93.57	80	100	529.1	87.03	0.1645	0.2963
103.14	90.03	0.1	103.4	42.87	0.4148	61.84
103.93	90.03	0.15	111.5	45.67	0.4097	44.38
105.71	90.02	0.22	121.1	46.61	0.3847	32.6
108.25	90.01	0.32	132.4	47.91	0.3619	24.31
110.8	90.01	0.46	141.1	48.54	0.3441	17.92
113.36	90	0.68	154	50.1	0.3253	13.16
114.68	90	1	168.9	51.26	0.3035	9.755
114.81	90	1.5	182.1	53.13	0.2917	6.989
115.16	90	2.2	193.7	54.26	0.2802	5.053
115.71	90	3.2	206.9	55.9	0.2702	3.701

116.26	90	4.6	219.1	56.97	0.26	2.719
116.81	90	6.8	232.8	58.16	0.2498	1.95
117.13	90	10	247.2	59.48	0.2406	1.405
117.33	90	14.6	259.9	60.92	0.2344	1.01
117.55	90	21.5	273.9	62.42	0.2279	0.7221
117.77	90	31.6	287.2	64.15	0.2234	0.5146
118.07	90	46.4	301.1	69.97	0.2324	0.3682
118.27	90	68	309.8	65.13	0.2102	0.2573
118.37	90	100	350.2	85.97	0.2455	0.1993
128.24	100.03	0.1	7.947	6.74	0.8482	5.758
129.04	100.03	0.15	9.037	7.4	0.8188	4.303
130.83	100.02	0.22	10.52	8.567	0.8145	3.407
133.36	100.01	0.32	12.63	10.33	0.818	2.819